APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 USC 156 FOR U.S. PATENT NO. 5,795,911

Applicants	:	Mitsui Norin Co., Ltd.; and Cancer Institute (Hospital), Chinese Academy of Medical Sciences
Patent Issue Date	:	August 18, 1998
Application Serial No.	:	08/835,920
Application Filing Date	:	April 10, 1997
Inventors	:	Shu Jung CHENG; De Chang WANG; and Yukihiko HARA
For	:	COMPOSITION FOR TREATING *CONDYLOMA ACUMINATA*
Attorneys for Applicants	:	Frishauf, Holtz, Goodman & Chick, P.C. 220 Fifth Avenue, 16th Floor New York, New York 10001-7708 E-Mail Address: BARTH@FHGC-LAW.COM
Customer No.	:	01933
Attorney Docket No.	:	970232EXT/HG

* * *

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APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 USC 156

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Applicants	:	Mitsui Norin Co., Ltd.; and Cancer Institute (Hospital), Chinese Academy of Medical Sciences
U.S. Patent No.	:	5,795,911
Issue Date	:	August 18, 1998
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Inventors	:	Shu Jung CHENG; De Chang WANG; and Yukihiko HARA
For	:	COMPOSITION FOR TREATING *CONDYLOMA ACUMINATA*
Attorneys for Applicants	:	Frishauf, Holtz, Goodman & Chick, P.C.
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APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 USC 156

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

MAIL STOP PATENT EXT.

S I R :

Pursuant to 201(a) of the Drug Price Competition and Patent Term Restoration Act of 1984, and in accordance with the

provisions of 35 USC 156, Mitsui Norin Co., Ltd., a corporation of Japan, having a place of business at 1-2-9, Nishishinbashi, Minato-ku, Tokyo 105-8427 Japan and Cancer Institute (Hospital), Chinese Academy of Medical Sciences, a corporation of the People's Republic of China, having a place of business at Panjiayuan No. 17, Chaoyang District, Beijing 100021, People's Republic of China (hereinafter referred to collectively as "Applicants"), the assignees of record of United States Patent No. 5,795,911, hereby apply for an extension of 1,300 days of the term of United States Patent No. 5,795,911 issued August 18, 1998 on patent application Serial No. 08/835,920 filed April 10, 1997.

The following information is submitted in accordance with 35 USC 156(d) and 37 CFR 1.740, and follows the numerical format set forth in 37 CFR 1.740.

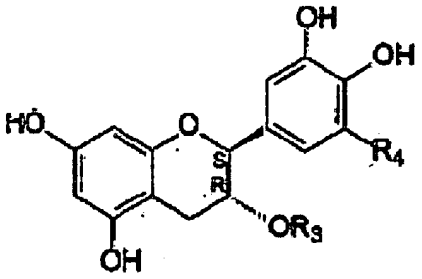
(1) A complete identification of the approved product as by appropriate chemical and generic name, physical structure and characteristics;

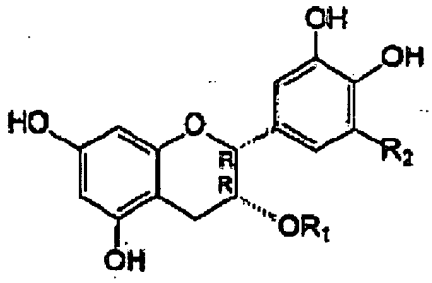
VEREGEN™ is a botanical drug product for topical use. The drug substance in VEREGEN™ is kunecatechins, which is a partially purified fraction of the water extract of green tea leaves from *Camellia sinensis (L.) O Kuntze*, and is a mixture of catechins and other green tea components. Catechins constitute 85 to 95% (by weight) of the total drug substance which includes more than 55% of Epigallocatechin gallate (EGCg), other catechin derivatives such as Epicatechin (EC), Epigallocatechin (EGC), Epicatechin gallate (ECg) and some additional minor catechin derivatives, i.e., Gallocatechin gallate (GCg), Gallocatechin (GC), Catechin gallate (Cg), and Catechin (C). In addition to the known catechin components, it also contains gallic acid, caffeine, and theobromine, which together constitute about 2.5% of the drug substance. The remaining amount of the drug

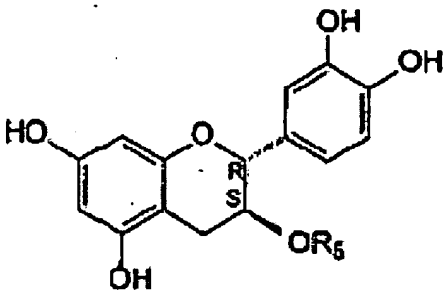
substance contains undefined botanical constituents derived from green tea leaves.

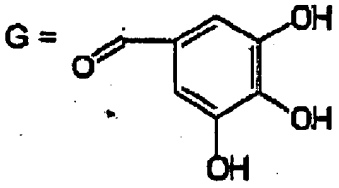
The structural formula of catechins is shown below. The proposed pharmacological class is immuno-modulatory.

General Structure of Catechins









Component	Abbrev.	R1	R2	R3	R4	R5
(−)-Epigallocatechin Gallate	(−)-EGCg	G	OH		–	–
(−)-Epicatechin Gallate	(−)-ECg	G	H		–	–
(−)-Epigallocatechin	(−)-EGC	H	OH	–		–
(−)-Epicatechin	(−)-EC	H	H	–	–	
(−)-Gallocatechin Gallate	(−)-GCg	–	–	G	OH	–
(−)-Gallocatechin	(−)-GC	–	–	H	OH	–
(−)-Catechin Gallate	(−)-Cg	–	–	G	H	–
(+)-Catechin	(+)-C	–		–	–	H

Each gram of the ointment (VEREGEN™ (kunecatechins) Ointment, 15% (also known as POLYPHENON® E Ointment, 15%)) contains 150 mg of kunecatechins in a water-free ointment base consisting of isopropyl myristate, white petrolatum, cera alba (white wax), propylene glycol palmitostearate and oleyl alcohol.

POLYPHENON® is a registered trademark of Mitsui Norin Co., Ltd. POLYPHENON E™ is a trademark of Mitsui Norin Co., Ltd. The VEREGEN™ trademark is used by Bradley Pharmaceuticals under a license from MediGene AG.

MediGene AG, which has a place of business at Lochhamer Str. 11, D-82152 Planegg/Martinsried, Germany, is an exclusive licensee of U.S. Patent No. 5,795,911 by virtue of a license agreement with Epitome Pharmaceuticals Limited. Epitome Pharmaceuticals Limited, having a place of business at 5162 Duke Street, Ste 500, Halifax, NS B3J 1N7 Canada, is a licensee of U.S. Patent No. 5,795,911 by virtue of a license agreement with Mitsui Norin Co., Ltd., a record owner of U.S. Patent No. 5,795,911.

A LETTER OF THE LICENSEE for each of MediGene AG and Epitome Pharmaceuticals Limited (attached hereto as Exhibits 1A and 1B, respectively) is being submitted concomitantly herewith, which provides authorization to the Applicants to rely on the activities and data of MediGene AG and Epitome Pharmaceuticals Limited before the Food and Drug Administration in obtaining approval of VEREGEN™ (kunecatechins) Ointment, 15% (also known as POLYPHENON® E Ointment, 15%) for the purpose of obtaining a patent term extension for United States Patent No. 5,795,911.

The Product Information Sheet for the approved product is the PACKAGE INSERT. A copy of the PACKAGE INSERT for the VEREGEN™ Ointment, 15% is attached hereto as Exhibit 2.

(2) A complete identification of the Federal Statute including the applicable provision of law under which the regulatory review occurred;

The regulatory review occurred under Section 505(b) of the Federal Food, Drug and Cosmetic Act ("FFDCA"), 21 USC 301, et seq. Section 505 provides for the submission and approval of new drug applications ("NDAs") for products.

(3) An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred;

VEREGEN™ (kunecatechins) Ointment, 15% (POLYPHENON® E Ointment, 15%) was approved by the Food and Drug Administration ("FDA") for commercial marketing pursuant to §505(b) of the FFDCA on October 31, 2006 (see Exhibit 3 (APPROVAL LETTER)).

(4) In the case of a human drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or

in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved;

The above ingredient in VEREGEN™ (kunecatechins) Ointment, 15% (POLYPHENON® E Ointment, 15%) comprises a mixture of polyphenols derived from a species of green tea, namely *Camellia sinensis*, by water extraction and fractionation by column chromatography. The active ingredient in VEREGEN™ (kunecatechins) Ointment, 15% (POLYPHENON® E Ointment, 15%) has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

(5) A statement that the application is being submitted within the sixty (60) day period permitted for submission pursuant to §1.720(f) and an identification of the date of the last day on which the application could be submitted;

The product was approved for commercial marketing on October 31, 2006, and the last day within the sixty (60) day period permitted for submission of an application for extension (pursuant to 37 CFR 1.720(f)) of the patent is December 30, 2006. The date of submission of the present application is no later than December 30, 2006 and, therefore, the present application has been timely filed.

(6) A complete identification of the patent for which an extension is being sought by the name of the inventors, the patent number, the date of issue, and the date of expiration:

U.S. Patent No.	:	5,795,911
Issue Date	:	August 18, 1998
Inventors	:	Shu Jun Cheng; De Chang Wang; Yukihiko Hara
Title	:	COMPOSITION FOR TREATING *CONDYLOMA ACUMINATA*
Application Serial No.	:	08/835,920
Application Filing Date	:	April 10, 1997
Expiration Date (unless extended)	:	April 10, 2017

The application was assigned from the inventors to the Applicants by an Assignment recorded on April 10, 1997 in the United States Patent and Trademark Office at Reel 8498, Frame 0028. A copy of the Recorded Assignment for USP 5,795,911 is attached herewith as Exhibit 4.

A correction of the address of Mitsui Norin Co., Ltd. was recorded in the United States Patent and Trademark Office on September 15, 1997 at Reel 8696, Frame 0607. A Change of Name Due to Merger (changing the name of Mitsui Norin Co., Ltd. to Nittoh Food Co., Ltd.) was recorded in the United States Patent and Trademark Office on September 29, 2003 at Reel 014532, Frame 0308. A Change of Name (changing the name of Nittoh Food Co., Ltd. back to Mitsui Norin Co., Ltd.) was recorded in the United States Patent and Trademark Office on October 6, 2003 at Reel 014546, Frame 0842. A Change of Address of Assignee (Mitsui Norin Co., Ltd.) was recorded at the United States Patent and Trademark Office on September 27, 2005 at Reel 016844, Frame 0058.

(7) A copy of the patent for which an extension is being sought, including the entire specification (including claims);

A copy of U.S. Patent No. 5,795,911 is attached as Exhibit 5 (PATENT).

(8) A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent;

No disclaimer or reexamination certificate has been issued.

A Certificate of Correction for United States Patent No. 5,795,911 was issued on November 19, 1999. A copy of said Certificate of Correction is attached herewith as Exhibit 6.

Two maintenance fee payments were made to the United States Patent and Trademark Office for United States Patent No. 5,795,911. Copies of each of the receipts for such maintenance fee payments, received from the United States Patent and Trademark Office, are attached hereto as Exhibits 7A and 7B.

(9) A statement that the patent claims the approved product, or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which at least one patent claim reads on:

(i) The approved product, if the listed claims include any claim to the approved product;

(ii) The method of using the approved product, if the listed claims include any claims to the method of using the approved product; and

(iii) The method of manufacturing the approved product, if the listed claims include any claim to the method of manufacturing the approved product;

The approved product VEREGEN™ (kunecatechins) Ointment, 15% (POLYPHENON® E Ointment, 15%), which comprises a tea catechin, has been approved for treating external genital and perianal warts (*Condyloma acuminata*) in immunocompetent patients 18 years or older.

The following claims 1, 2, 3, 5, 6, 7, 10, 11, 13 and 14 of U.S. Patent No. 5,795,911 include the approved use of the approved product.

1. A method of treating *Condyloma acuminata* caused by human papillomavirus, comprising applying to an infected area on a human a composition which comprises a tea catechin as a main component in an amount effective for treating *Condyloma acuminata*.

2. The method according to claim 1, wherein the composition is in the form of an ointment or a suppository.

3. The method according to claim 1, wherein said composition is in the form of an ointment having 5-20% by weight of tea catechin.

5. The method according to claim 1, wherein said tea catechin comprises (-)-epigallocatechin.

6. The method according to claim 3, wherein the tea catechin is in an amount of 12-18% by weight.

7. The method according to claim 3, wherein the tea catechin is in an amount of 15% by weight.

10. The method according to claim 3, wherein the ointment contains vaseline as a base to form a cream.

11. The method according to claim 3,wherein the ointment is applied to external genital organs.

14. The method according to claim 1, wherein the infected area is an external genital organ.

Claim 1

Claim 1 recites a method of treating *Condyloma acuminata* comprising applying to an infected area a composition which comprises a tea catechin. Claim 1 thus recites the active ingredient of the approved product, namely a catechin, for the approved use, namely treating *Condyloma acuminata*.

Claim 2

In claim 2, which depends on claim 1, an ointment is recited. The approved product is an ointment.

Claim 3

In claim 3, which depends on claim 1, an ointment having 5-20% by weight of tea catechin is recited. The approved product has 15% by weight of tea catechin.

Claim 5

In claim 5, which depends on claim 1, it is recited that the tea catechin comprises (-)-epigallocatechin. The approved product contains (-)-epigallocatechin.

Claim 6

In claim 6, which depends on claim 3, 12-18% by weight of tea catechin is recited. The approved product has 15% by weight of tea catechin.

Claim 7

In claim 7, which depends on claim 3 due to its correction in the Certificate of Correction for United States Patent No. 5,795,911, issued on November 23, 1999, 15% by weight of tea catechin is recited. The approved product has 15% by weight of tea catechin.

Claim 10

Claim 10 depends on claim 3 and recites that the ointment contains vaseline. The approved product includes white petrolatum.

Claims 11 and 14

Claim 11 depends on claim 3 and recites that the ointment is applied to external genital organs.

Claim 14 depends on claim 1 and recites that the infected area is an external genital organ.

The approved use covers application of the approved product to an external genital organ.

(10) A statement beginning on a new page of the relevant dates and information pursuant to 35 USC 156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period as follows:

(i) For a patent claiming a human drug, antibiotic or human biological product:

(A) The effective date of the investigational new drug (IND) application and the IND number;

(B) The date on which a new drug application (NDA) or a Product License Application (PLA) was initially submitted and the NDA or PLA number; and

(C) The date on which the NDA was approved or the Product License issued;

On July 7, 1998, a "Notice of Claimed Investigational Exemption for a New Drug" ("IND") was submitted to the Food and Drug Administration (hereinafter sometimes referred to as the "FDA") for POLYPHENON® E Ointment, 15%. A copy of the IND submission letter is submitted herewith as Exhibit 8 (IND SUBMISSION LETTER).

The IND was assigned number 56,401. The IND became effective on August 13, 1998, which is thirty (30) days after receipt of the IND by the FDA, i.e., July 14, 1998. A copy of the IND acknowledgment letter is submitted herewith as Exhibit 9 (IND ACKNOWLEDGMENT LETTER).

This establishes the beginning of the "regulatory review period" under 35 USC 156(g)(1) as of August 13, 1998.

On September 23, 2005, a new drug application (NDA 21-902) was submitted under §505(b) of the Federal Food, Drug and Cosmetic Act (FDDCA) and §314.50 of Title 21 of the Code of

Federal Regulations for POLYPHENON® E Ointment, 15%. A copy of the September 23, 2005 letter attached to NDA 21-902 is provided herewith as Exhibit 10 (NDA SUBMISSION LETTER).

NDA 21-902 for VEREGEN™ (kunecatechins) Ointment, 15% (POLYPHENON® E Ointment, 15%) was approved on October 31, 2006. Attached as Exhibit 3 (APPROVAL LETTER) is a copy of a letter dated October 31, 2006 from the FDA approving NDA 21-902 for VEREGEN™ (kunecatechins) Ointment, 15% (POLYPHENON® E Ointment, 15%).

Thus, for the purposes of determining the "regulatory review period" under 35 USC §156(g)(1), October 31, 2006 is the date of the first approval of VEREGEN™ (kunecatechins) Ointment, 15% (POLYPHENON® E Ointment, 15%).

Summary of the Most Relevant Dates

July 7, 1998 : IND for POLYPHENON® E Ointment, 15% submitted

July 14, 1998	:	Receipt by the FDA of the IND for POLYPHENON® E Ointment, 15%
August 13, 1998	:	IND 56,401 for POLYPHENON® E Ointment, 15% became effective
September 23, 2005	:	NDA 21-902 for POLYPHENON® E Ointment, 15% was submitted
October 31, 2006	:	NDA 21-902 for VEREGEN™ (kunecatechins) Ointment, 15% (POLYPHENON® E Ointment, 15%) was approved

(11) A brief description, beginning on a new page, of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities.

As described above, in item (10) hereinabove, an IND for POLYPHENON® E Ointment, 15% was submitted on July 7, 1998, which became effective on August 13, 1998. The studies under the IND are summarized in the attached Exhibit 11 (IND LOG). These studies were used to support NDA 21-902 which was submitted on September 23, 2005.

Subsequent to the submission of the aforesaid NDA, personnel of the applicants have had numerous contacts and meetings with FDA personnel with respect to the new drug application, and these are summarized in the attached Exhibit 12 (NDA LOG).

(12) A statement, beginning on a new page, that in the opinion of the Applicants the patent is eligible for the extension and a statement as to the length of the extension claimed, including how the length of extension was determined;

Statement of Eligibility of the Patent for Extension Under §35 USC 156(a) and (c)(4)

Section 156(a) provides, in relevant part, that the term of a patent which claims a product, a method of using a product or a method of manufacturing a product shall be extended if (1) the term of the patent has not expired before an application for extension is submitted, (2) the term of the patent has never been extended, (3) the application for extension is submitted by the owner of record of the patent or its agent in accordance with 35 USC §156(d), (4) the product has been subject to a regulatory review period before its commercial marketing or use, and (5) the permission for commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period

occurred; and §156(c)(4) provides, that in no event shall more than one patent be extended for the same regulatory review period for any product.

As described by corresponding letters, each of these elements is satisfied herein as follows:

(a) The statutory term of U.S. Patent No. 5,795,911 expires on April 10, 2017. This Application for Extension of Patent Term has, therefore, been submitted before the expiration of the patent term.

(b) The term of this patent has never been extended.

(c) This Application for Extension of Patent Term is submitted by the owners of record, namely Mitsui Norin Co., Ltd. and Cancer Institute (Hospital), Chinese Academy of Medical Sciences. This Application for Extension of Patent Term is submitted in accordance with 35 USC §156(d) in that it is submitted within the sixty (60) day period beginning on the date, October 31, 2006, that the product received permission for

marketing under the Federal Food, Drug and Cosmetic Act and contains the information required under 35 USC §156(d).

(d) As evidenced by the October 31, 2006 letter from the FDA, Exhibit 3 (APPROVAL LETTER), the product was subject to a regultory review period under §505(b)(1) of the FFDCA before its commercial marketing or use.

(e) The permission for the commercial marketing of VEREGEN™ (kunecatechins) Ointment, 15% (POLYPHENON® E Ointment, 15%) after regulatory review under §505(b)(1) is the first permitted commercial marketing of VEREGEN™ (kunecatechins) Ointment, 15% (POLYPHENON® E Ointment, 15%). This is confirmed by the absence of any approved new drug application under which VEREGEN™ (kunecatechins) Ointment, 15% (POLYPHENON® E Ointment, 15%) could be commercially marketed prior to October 31, 2006.

Statement as to Length of Extension Claimed in Accordance with 37 USC §1.775

The term of U.S. Patent No. 5,795,911 should be extended for a period of 1,300 days to extend to October 31, 2020.

The period of extension is determined in accordance with 35 USC §156 and follows the format set forth in 37 CFR 1.775(c) and (d).

37 CFR §1.775(c). The length of the regulatory review period for a human drug, antibiotic drug or human biological product will be determined by the Secretary of Health and Human Services. Under 35 USC §156(g)(1)(B), it is the sum of:

(1) The number of days in the period beginning on the date an exemption under subsection (i) of section 505 or subsection (d) of section 507 of the Federal Food, Drug and Cosmetic Act became effective for the approved product and ending on the date the application was initially submitted for such product under

those sections or under section 351 of the Public Health Service Act;

The number of days between the effective date of the initial IND, August 13, 1998, and the initial submission of NDA 21-902, September 23, 2005, is a period of 2,598 days, and

(2) The number of days in the period beginning on the date the application was initially submitted for the approved product under section 351 of the Public Health Service Act, subsection (b) of section 505 or section 507 of the Federal Food Drug and Cosmetic Act and ending on the date such application was approved under such section.

The number of days between the initial submission of NDA 21-902 on September 23, 2005, to approval of NDA 21-902 on October 31, 2006 is a period of 403 days.

37 CFR §1.775(d). The term of the patent as extended for a human drug, antibiotic drug or human biological product will be determined by -

(1) Subtracting from the number of days determined by the Secretary of Health and Human Services to be in the regulatory review period;

(i) The number of days in the period of paragraphs (c)(1) and (c)(2) of this section which were on and before the date on which the patent issued;

The number of days in the period of the IND, effective on August 13, 1998, which were on or before August 18, 1998, the date the patent issued, is a period of 5 days;

2598 days minus 5 days equals 2,593 days, and

the number of days in the period of the NDA initial submission of NDA 21-902 on September 23, 2005, and approval on October 31, 2006 which were on or before August 18, 1998, the date the patent issued, is a period of 0 days.
403 days minus 0 days equals 403 days.

(ii) The number of days in the periods of paragraphs (c)(1) and (c)(2) of this section during which it is determined under 35 USC 156(d)(2)(B) by the Secretary of Health and Human Services that applicant did not act with due diligence;

The number of days the Applicant did not act with due diligence is 0 days, therefore

2,593 days minus 0 days equals 2,593 days;

403 days minus 0 days equals 403 days.

(iii) One-half the number of days remaining in the the period defined by paragraph (c)(1) of this section after that period is reduced in accordance with paragraphs (d)(1)(i) and (ii) of this section; half days will be ignored for purposes of subtraction;

One-half of 2,593 days equals 1,296 days.

(2) By adding the number of days determined in paragraph (d)(1) of this section to the original term of the patent, as shortened by any terminal disclaimer;

403 days + 1,296 days = 1,699 days.

Adding 1,699 days to April 10, 2017, the original term of the patent (no terminal disclaimer was made), extends the term to December 5, 2021.

(3) By adding 14 years to the date of approval of the application under section 351 of the Public Health Service Act, or subsection (b) of

section 505 or 507 of the Federal Food, Drug and Cosmetic Act;

Adding 14 years to October 31, 2006, the date of approval of the Application, results in the date of October 31, 2020.

(4) By comparing the dates for the ends of the periods obtained pursuant to paragraphs (d)(2) and (d)(3) of this section with each other and selecting the earlier date;

The earlier date is October 31, 2020.

(5) If the original patent was issued after September 24, 1984,

(i) By adding 5 years to the original expiration date of the patent or any earlier date set by terminal disclaimer; and

Adding 5 years to the original expiration date of the patent (April 10, 2017) results in the date of April 10, 2022.

(ii) By comparing the dates obtained pursuant to paragraphs (d)(4) and (d)(5)(i) of this section with each other and selecting the earlier date;

Comparing October 31, 2020 and April 10, 2022, the earlier date is October 31, 2020 and therefore the patent term should be extended to October 31, 2020.

(6) If the original patent was issued before September 24, 1984, and ....

This is not applicable for the above-identified patent.

(13) A statement that Applicant acknowledges a duty to disclose to the Commissioner for Patents and Trademarks and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought (see §1.765);

Applicants acknowledge a duty to disclose to the Commissioner for Patents and Trademarks and to the Secretary of Health and Human Services any information which is material to any determination to be made relative to the application for extension.

Other than the information set forth hereinabove and submitted herewith, Applicants are unaware of any additional information material to this Application for Extension of Patent Term.

(14) The prescribed fee for receiving and acting upon the application for extension (see §1.20(j));

Form PTO-2038 in the amount of One Thousand One Hundred Twenty Dollars ($1,120) in payment of the prescribed fee for receiving and acting upon the application for extension is enclosed herewith.

(15) The name, address and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed:

Richard S. Barth, Esq.
Frishauf, Holtz, Goodman
& Chick, P.C.
220 Fifth Avenue, 16th Fl.
New York, NY 10001-7708
Tel. No. (212) 319-4900
Fax No.: (212) 319-5101
E-Mail: BARTH@FHGC-LAW.COM.

This application is being signed by the undersigned registered practitioner on behalf of the patent owners.

Frishauf, Holtz, Goodman
& Chick, P.C.
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Respectfully submitted,

Richard S. Barth
Reg. No. 28,180

RSB/ddf

EXHIBIT 1A
LETTER OF LICENSEE
OF MEDIGENE AG

MediGene

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

MAIL STOP PATENT EXT.

Martinsried, November 7, 2006
CR

Re: Application for Extension of Patent Term
Under 35 USC 156 for U.S. Patent No. 5,795,911

S I R:

I, Peter Heinrich, Chief Executive Officer of MediGene AG, state as follows:

1. MediGene AG has a place of business at Lochhamer Str. 11, D-82152, Planegg/Martinsried, Germany.

2. MediGene AG is an exclusive licensee of U.S. Patent No. 5,795,911 by virtue of a license agreement with Epitome Pharmaceuticals Limited. Epitome Pharmaceuticals Limited is an exclusive licensee of U.S. Patent No. 5,795,911 by virtue of a license agreement with Mitsui Norin Co., Ltd., a record owner of U.S. Patent No. 5,795,911.

3. U.S. Patent No. 5,795,911 claims treating *Condyloma acuminata* comprising applying to an infected area on a human a composition which comprises a tea catechin.

4. U.S. Patent No. 5,795,911 covers the use of Polyphenon E, 15%, also know as "VEREGEN" (which contains a tea catechin) to treat genital warts (*Condyloma acuminata*).

5. MediGene AG, in conjunction with Epitome Pharmaceuticals Limited, participated in the clinical evaluation and registration of Polyphenon E, 15%, pursuant to NDA 21-902. NDA 21-902 was submitted to the Food and Drug Administration by MediGene, Inc.

6. The relationship between MediGene AG and MediGene, Inc. is as follows: MediGene, Inc. is a fully owned subsidiary of MediGene AG.

7. MediGene AG hereby authorizes Mitsui Norin Co., Ltd. and Cancer Institute (Hospital), Chinese Academy of Medical Sciences to rely on the activities of MediGene AG and MediGene, Inc. pursuant to NDA 21-902 to file an application under 35 U.S.C. §156 for extension of U.S. Patent No. 5,795,911.

Very truly yours,

Peter Heinrich

EXHIBIT 1B
LETTER OF LICENSEE OF
EPITOME PHARMACEUTICALS LIMITED

EPITOME
PHARMACEUTICALS

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

MAIL STOP PATENT EXT.

Re: Application for Extension of Patent Term
Under 35 USC 156 for U.S. Patent No. 5,795,911

Dear Sir or Madam,

I, Paul T. Wegener, President of Epitome Pharmaceuticals Limited, having authority to act on behalf of Epitome Pharmaceuticals Limited state as follows:

1. Epitome Pharmaceuticals Limited has a place of business at 5162 Duke Street, Ste 500, Halifax, NS B3J 1N7 Canada.

2. Epitome Pharmaceuticals Limited is a licensee of U.S. Patent No. 5,795,911 by virtue of a license agreement with Mitsui Norin Co., Ltd., a record owner of U.S. Patent No. 5,795,911.

3. U.S. Patent No. 5,795,911 claims treating Condyloma acuminata comprising applying to an infected area on a human a composition which comprises a tea catechin.

4. U.S. Patent No. 5,795,911 covers the use of Polyphenon E, 15%, also known as VEREGEN, (which contains a tea catechin) to treat genital warts (Condyloma acuminata). IND No. 56,401 for Polyphenon Ointment was filed by Epitome Pharmaceuticals Limited.

5. Epitome Pharmaceuticals Limited, in conjunction with MediGene AG, participated in the clinical evaluation and registration of Polyphenon E, 15%, pursuant to NDA 21-902. NDA 21-902 was submitted to the Food and Drug Administration by MediGene, Inc. MediGene AG is a licensee of U.S. Patent No. 5,795,911 by virtue of a license agreement with Epitome Pharmaceuticals Limited.

6. Epitome Pharmaceuticals Limited hereby authorizes Mitsui Norin Co., Ltd. and Cancer Institute (Hospital), Chinese Academy of Medical Sciences to rely on the activities of Epitome Pharmaceuticals Limited pursuant to IND 56401 and NDA 21-902 to file an application under 35 U.S.C. §156 for extension of U.S. Patent No. 5,795,911.

Very truly yours,

Paul T. Wegener

5162 DUKE STREET, SUITE 500, HALIFAX, NOVA SCOTIA B3J 1N7 CANADA • PH: (902) 492-1814 • FX: (902) 492-0013

EXHIBIT 2
PACKAGE INSERT

VEREGEN™

(Kunecatechins)

Ointment, 15%

Rx Only

For Topical Dermatologic Use Only

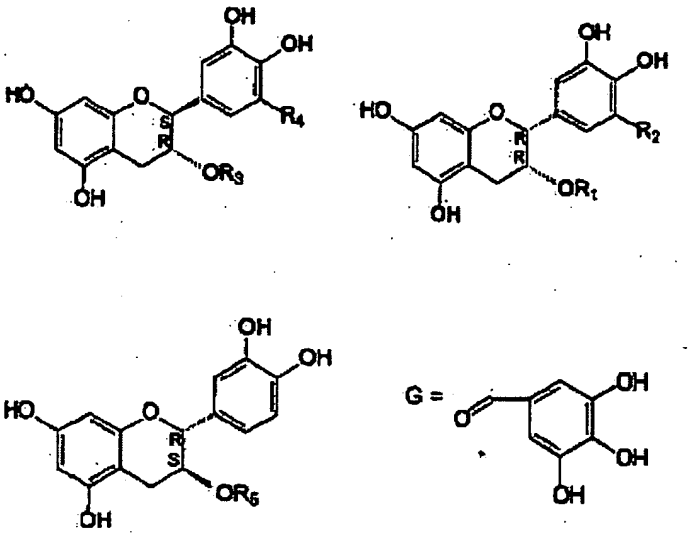
Not for Ophthalmic, Oral, Intravaginal, or Intra-anal Use

DESCRIPTION

Veregen™ is a botanical drug product for topical use. The drug substance in Veregen is Kunecatechins, which is a partially purified fraction of the water extract of green tea leaves from *Camellia sinensis (L.) O Kuntze*, and is a mixture of catechins and other green tea components. Catechins constitute 85 to 95% (by weight) of the total drug substance which includes more than 55% of Epigallocatechin gallate (EGCg), other catechin derivatives such as Epicatechin (EC), Epigallocatechin (EGC), Epicatechin gallate (ECg) and some additional minor catechin derivatives i.e. Gallocatechin gallate (GCg), Gallocatechin (GC), Catechin gallate (Cg), and Catechin (C). In addition to the known catechin components, it also contains gallic acid, caffeine, and theobromine which together constitute about 2.5% of the drug substance. The remaining amount of the drug substance contains undefined botanical constituents derived from green tea leaves.

The structural formulae of catechins are shown below.

General Structure of Catechins



Component	Abbrev.	R1	R2	R3	R4	R5
(+)-Epigallocatechin Gallate	(-)-EGCg	G	OH		-	-
(+)-Epicatechin Gallate	(-)-ECg	G	H		-	-
(+)-Epigallocatechin	(-)-EGC	H	OH	-	-	-
(+)-Epicatechin	(-)-EC	H	H	-	-	
(+)-Gallocatechin Gallate	(+)-GCg	-	-	G	OH	-
(+)-Gallocatechin	(-)-GC	-	-	H	OH	-
(+)-Catechin Gallate	(-)-Cg	-	-	G	H	-
(+)-Catechin	(+)-C	-		-	-	H

Each gram of the ointment contains 150 mg of Kunecatechins in a water free ointment base consisting of isopropyl myristate, white petrolatum, cera alba (white wax), propylene glycol palmitostearate, and oleyl alcohol.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mode of action of Veregen™ Ointment, 15% involved in the clearance of genital and perianal warts is unknown. In vitro, Kunecatechins had anti-oxidative activity; the clinical significance of this finding is unknown.

Pharmacokinetics

The pharmacokinetics of topically applied Veregen Ointment has not been sufficiently characterized at this time. However, data suggest that systemic exposure to catechins after repeated topical application of Veregen Ointment 15% is likely to be less than observed after a single oral intake of 400ml green tea.

CLINICAL STUDIES

Two Phase 3 randomized, double-blind, vehicle-controlled studies were performed to investigate the safety and efficacy of Veregen™ Ointment in the treatment of immunocompetent patients 18 years of age and older with external genital and perianal warts. The subjects applied the ointment 3 times daily for up to 16 weeks or until complete clearance of all warts (baseline and new warts occurring during treatment).

Over both studies the median baseline wart area was 51 mm^2 (range 12 to 585 mm^2), and the median baseline number of warts was 6 (range 2 to 30).

The primary efficacy outcome measure was the response rate defined as the proportion of patients with complete clinical (visual) clearance of all external genital and perianal warts (baseline and new) by week 16, presented in Tables 1 and 2 for all randomized subjects dispensed medication.

Table 1: Efficacy by Region

	Complete Clearance
All Countries (includes the United States)	
Veregen™ 15% (*N* = 397)	213 (53.6%)
Vehicle (*N* = 207)	73 (35.3%)
United States	
Veregen™ 15% (*N* = 21)	5 (23.8%)
Vehicle (*N* = 9)	0 (0.0%)

Table 2. Efficacy by Gender

	Complete Clearance
Males	
Veregen™ 15% (*N* = 205)	97 (47.3%)
Vehicle (*N* = 118)	34 (28.8%)
Females	
Veregen™ 15% (*N* = 192)	116 (60.4%)
Vehicle (*N* = 89)	39 (43.8%)

Median time to complete wart clearance was 16 weeks and 10 weeks, respectively, in the two phase 3 clinical trials.

The incidence rate of recurrence of external genital and perianal warts after treatment in patients with complete clearance is unknown.

INDICATION AND USAGE

Veregen™ is indicated for the topical treatment of external genital and perianal warts (*Condylomata acuminata*) in immunocompetent patients 18 years and older.

CONTRAINDICATIONS

Veregen™ is contraindicated in individuals with a history of sensitivity reactions to any of the components of the ointment. In case of hypersensitivity, treatment should be discontinued.

WARNINGS

Veregen™ has not been evaluated for the treatment of urethral, intra-vaginal, cervical, rectal, or intra-anal human papilloma viral disease and should not be used for the treatment of these conditions.

PRECAUTIONS

General

Use of Veregen™ on open wounds should be avoided.
The safety and efficacy of Veregen™ in immunosuppressed patients have not been established.
Safety and efficacy have not been established for Veregen™ in the treatment of external genital and perianal warts beyond 16-weeks or for multiple treatment courses.
Patients should be advised to avoid exposure of the genital and perianal area to sun/UV-light as Veregen™ has not been tested under these circumstances.

Information for Patients

General Information

Patients using Veregen™ should receive the following information and instructions:

1. This medication is only to be used as directed by a physician. It is for external use only. Eye contact should be avoided as well as application into the vagina or anus.
2. It is not necessary to wash off Veregen™ prior to the next application. When the treatment area is washed or a bath is taken, the ointment should be applied afterwards.
3. It is common for patients to experience local skin reactions such as erythema, erosion, edema, itching, and burning at the site of application. Severe skin reactions can occur and should be promptly reported to the healthcare provider. Should severe local skin reaction occur, the ointment should be removed by washing the treatment area with mild soap and water and further doses held.
4. Sexual (genital, anal or oral) contact should be avoided while the ointment is on the skin, or the ointment should be washed off prior to these activities. Veregen™ may weaken condoms and vaginal diaphragms. Therefore the use in combination with Veregen™ is not recommended.
5. Female patients using tampons should insert the tampon before applying the ointment. If the tampon is changed while the ointment is on the skin, accidental application of the ointment into the vagina must be avoided.
6. Veregen™ may stain clothing and bedding.
7. Veregen™ is not a cure and new warts might develop during or after a course of therapy. If new warts develop during the 16 –week treatment period, these should also be treated with Veregen™.
8. The effect of Veregen™ on the transmission of genital/perianal warts is unknown.
9. Patients should be advised to avoid exposure of the genital and perianal area to sun/UV light as Veregen™ has not been tested under these circumstances.
10. The treatment area should not be bandaged or otherwise covered or wrapped as to be occlusive.
11. Uncircumcised males treating warts under the foreskin should retract the foreskin and clean the area daily.

Carcinogenesis, Mutagenesis, Impairment of Fertility
The Maximum Recommended Human Dose (MRHD) of Veregen™ Ointment, 15% was set at three times daily topical administration of 250 mg, 750 mg total, containing 112.5 mg Kunecatechins for the animal multiple of human exposure calculations presented in this labeling. Dose multiples were calculated based on the human equivalent dose (HED).

In an oral (gavage) carcinogenicity study, Kunecatechins was administered daily for 26 weeks to p53 transgenic mice at doses up to 500 mg/kg/day (22-fold MRHD). Treatment with Kunecatechins was not associated with an increased incidence of either neoplastic or non-neoplastic lesions in the organs and tissues examined. Veregen™ Ointment, 15% has not been evaluated in a dermal carcinogenicity study.

Kunecatechins was negative in the Ames test, in vivo rat micronucleus assay, UDS test, and transgenic mouse mutation assay, but positive in the mouse lymphoma mutation assay.

Daily vaginal administration of Veregen™ Ointment, 15% to rats from Day 4 before mating and throughout mating until Day 17 of gestation did not cause adverse effects on mating performance and fertility at doses up to 0.15 mL/rat/day. This dose corresponds to approximately 150 mg/rat/day (8-fold MRHD).

Pregnancy Category: C
Embryo-fetal development studies were conducted in rats and rabbits using intravaginal and systemic routes of administration, respectively. Oral administration of Kunecatechins during the period of organogenesis (gestational Days 6 to 15 in rats or 6 to 18 in rabbits) did not cause treatment related effects on embryo-fetal development or teratogenicity at doses of up to 1,000 mg/kg/day (86-fold MRHD in rats; 173-fold MRHD in rabbits).

In the presence of maternal toxicity (characterized by marked local irritation at the administration sites and decreased body weight and food consumption) in pregnant female rabbits, subcutaneous doses of 12 and 36 mg/kg/day of Kunecatechins during the period of organogenesis (gestational Days 6 to 19) resulted in corresponding influences on fetal development including reduced fetal body weights and delays in skeletal ossification. No treatment related effects on embryo-fetal development were noted at 4 mg/kg/day (0.7-fold MRHD). There was no evidence of teratogenic effects at any of the doses evaluated in this study.

A combined fertility / embryo-fetal development study using daily vaginal administration of Veregen™ Ointment, 15% to rats from Day 4 before mating and throughout mating until Day 17 of gestation did not show treatment-related effects on embryo-fetal development or teratogenicity at doses up to 0.15 mL/rat/day (8-fold MRHD).

A pre- and post-natal development study was conducted in rats using vaginal administration of Veregen™ Ointment, 15% at doses of 0.05, 0.10 and 0.15 mL/rat/day from Day 6 of gestation through parturition and lactation. The high and intermediate dose levels of 0.15 (8-fold MRHD) and 0.10 mL/rat/day resulted in an increased mortality of the F_0 dams, associated with indications of parturition complications. The high dose level of 0.15 mL/rat/day also resulted in an increased incidence of stillbirths. There were no other treatment-related effects on pre- and post-natal development, growth, reproduction and fertility at any dose tested.

There are no adequate and well-controlled studies in pregnant women. Veregen™ Ointment, 15% should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
It is not known whether topically applied Veregen™ is excreted in breast milk.

Pediatric Use
Safety and efficacy in pediatric patients have not been established.

Geriatric Use
Seven patients (1.4%), older than 65 years of age were treated with Veregen™ in clinical studies. This, however, is an insufficient number of subjects to determine whether they respond differently from younger subjects.

ADVERSE REACTIONS

ADVERSE EVENTS / LOCAL SKIN REACTIONS

In Phase 3 clinical trials, a total of 397 subjects received Veregen™ Ointment, 15% three times per day topical application for the treatment of external genital and perianal warts for up to 16 weeks.

Serious local adverse events of pain and inflammation were reported in two subjects (0.5%), both women.

In clinical trials, the incidence of local adverse events leading to discontinuation or dose interruption (reduction) was 5% (19/397). These included the following events: application site reactions (local pain, erythema, vesicles, skin erosion/ulceration), phimosis, inguinal lymphadenitis, urethral meatal stenosis, dysuria, genital herpes simples, vulvitis, hypersensitivity, pruritus, pyodermitis, skin ulcer, erosions in the urethral meatus, and superinfection of warts and ulcers.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect rates observed in practice.

Local and regional reactions (includes adenophathy) occurring at >1% in the treated group are presented in Table 3.

Table 3: Local and Regional Adverse Reactions During Treatment (% Subjects)

	Veregen *(N=397)*	Vehicle *(N=207)*
Erythema	70	32
Pruritus	69	45
Burning	67	31
Pain/discomfort	56	14
Erosion/Ulceration	49	10
Edema	45	11
Induration	35	11
Rash vesicular	20	6
Regional Lymphadenitis	3	1
Desquamation	5	<1
Discharge	3	<1
Bleeding	2	<1
Reaction	2	0
Scar	1	0
Irritation	1	0
Rash	1	0

A total of 266/397 (67%) of subjects in the Veregen, 15% group had either a moderate or a severe reaction that was considered probably related and of these 120 (30%) subjects had a severe reaction. Severe reactions occurred in 37% (71/192) of women and in 24% (49/205) of men. The percentage of subjects with at least one severe, related adverse event was 26% (86/328) for subjects with genital warts only, 42% (19/45) in subjects with both genital and perianal warts and 48% (11/23) of subjects with perianal warts only.

Phimosis occurred in 3% of uncircumcised male subjects (5/174) treated with Veregen and in 1% (1/99) in vehicle.

The maximum mean severity of erythema, erosion, edema and induration was observed by week 2 of treatment.

Less common local adverse events included urethritis, perianal infection, pigmentation changes, dryness, eczema, hyperesthesia, necrosis, papules, and discoloration. Other less common adverse events included cervical dysplasia, pelvic pain, cutaneous facial rash and staphylococcemia.

In a dermal sensitization study of Veregen ointment in healthy volunteers, hypersensitivity (type IV) was observed in 5 out of 209 subjects (2.4%) under occlusive conditions.

OVERDOSAGE

Overdosage with Veregen™ has not been reported.

DOSAGE AND ADMINISTRATION
Veregen™ Ointment, 15% is to be applied three times per day to all external genital and perianal warts.

It is recommended to wash the hands before and after application of Veregen™ About an 0.5 cm strand of the Veregen™ Ointment, 15% should be applied to each wart using the finger(s), dabbing it on to ensure complete coverage and leaving a thin layer of the ointment on the warts.

It is not necessary to wash off the ointment from the treated area prior to the next application.

Treatment with Veregen™ should be continued until complete clearance of all warts, however no longer than 16 weeks.

Local skin reactions (e.g. erythema) at the treatment site are frequent. Nevertheless, treatment should be continued when the severity of the local skin reaction is acceptable.

HOW SUPPLIED
Veregen™ ointment, 15% is a brown ointment and is supplied in aluminium tubes containing 15 gram ointment per tube.

Storage Conditions
Prior to dispensing to the patient, store refrigerated 2^0C to 8^0C (36^0F to 46^0F). After dispensing, store refrigerated or up to 25°C (77°F).
Do not freeze.
Keep out of reach of children

NDC # 10337-450-15

The VEREGEN trademark is used by Bradley Pharmaceuticals, Inc. under license from MediGene AG."

Manufactured by:
C.P.M. Contract Pharma GmbH & Co. KG
Frühlingstrasse 7
D-83620 Feldkirchen-Westerham
Germany

Manufactured for:

DOAK DERMATOLOGICS
A SUBSIDIARY OF BRADLEY PHARMACEUTICALS, INC.

383 Route 46 West
Fairfield, NJ 07004 2402 USA
Co-marketed with Kenwood Therapeutics, a division of Bradley Pharmaceuticals, Inc.

PATIENT INFORMATION

Veregen
(Kunecatechins)
Ointment, 15%

Rx Only

Read this leaflet carefully before you start using Veregen Ointment, 15% and each time you refill your prescription. There may be new information. This information does not take the place of your doctor's advice. If you have any questions about Veregen Ointment, 15% or your condition ask your doctor or pharmacist. Only your doctor can prescribe Veregen and determine if it is right for you.

What is Veregen Ointment, 15%?
Veregen Ointment, 15% is a medicine for skin use only (topical) for the treatment of warts on the outside of the genitals and around the outside of the anus caused by a virus known as the human papilloma virus (HPV) in adults. It is not a treatment for the HPV infection in the vagina, cervix, or inside the anus. Your doctor may recommend examination and screening tests (such as a Pap smear) to look for signs of the HPV infection in these areas.

Who should not use Veregen Ointment, 15%?
Do not use Veregen Ointment, 15% if you **are allergic** to an ingredient in Veregen Ointment, 15%. **The list of ingredients is at the end of this leaflet.**

What should I tell my doctor before taking Veregen Ointment, 15%?
Tell your doctor about all your health conditions and all the medicines you take including prescription, over-the-counter medicine, vitamins, supplements, and herbals. Be sure to tell your doctor if you are:

- **pregnant or planning to become pregnant,** as it is not known if Veregen Ointment, 15% can harm your unborn baby. Your doctor will determine whether the benefit outweighs the risk.
- **breastfeeding,** as it is not known if Veregen Ointment, 15% can pass into your milk and if it can harm your baby.
- **using any other type of skin product or have open wounds on the area to be treated.** Veregen Ointment, 15% should not be used until your skin has healed from other treatments applied to the same area.
- **immunocompromised**. This means that your immune system cannot fight infections as well as it should.

How should I use Veregen Ointment, 15%?

- Use Veregen Ointment, 15% only on the area affected **exactly** as prescribed by your doctor.

- **Wash your hands before and after application of Veregen Ointment, 15%.** A small amount of the ointment should be applied to all wart using your finger(s), dabbing it on to ensure complete coverage and leaving a thin layer of the ointment on the warts as directed by your doctor.

- **Apply Veregen Ointment, 15% three times per day —in the morning, at noontime and in the evening.**

- Do not wash off the ointment from the treated area before the next application. When you wash the treatment area or bathe, apply the ointment afterwards.

- Treatment with Veregen Ointment, 15% should be continued until complete clearance of all warts, however **no longer than 16 weeks.** If your warts do not go away, or if they come back after treatment call your doctor.

- Veregen Ointment, 15% is not a cure for warts on your genitals or around your anus with certainty. New warts may develop during or after treatment, and may need treatment.

What Should I Avoid While Using Veregen Ointment, 15%?

- Do not apply Veregen Ointment, 15% on open wounds or into the vagina or into the anus.

- Genital warts are a sexually transmitted disease, and you may infect your partner.

- Avoid sexual contact (genital, anal or oral) when Veregen Ointment, 15% is on your genital or perianal skin. If you do choose to have sexual contact, you must wash off the ointment carefully before having protected sexual contact as the ointment may weaken condoms and vaginal diaphragms. Talk to your doctor about safe sex practices.

- Avoid contact with your eyes, nostrils and mouth while ointment is on your finger(s).

- Women using tampons: insert the tampon before applying the ointment. If you need to change your tampon while the ointment is on your skin, avoid getting the ointment into the vagina.

- Uncircumcised men treating warts under the foreskin should retract the foreskin and clean the area daily.

- Do not expose the genital area treated with Veregen Ointment, 15% to sunlight, sunlamps or tanning beds.

- Do not cover the treated area. Loose-fitting undergarments can be worn after applying Veregen Ointment, 15%.

- Veregen Ointment, 15% may stain your light colored clothes and bedding. It is recommended to wear darker colored undergarments while using Veregen Ointment, 15%.

What are the possible side effects of Veregen Ointment, 15%?
The most common side effects with Veregen Ointment, 15% are local skin and application site reactions including:

- redness
- swelling
- sores or blisters
- burning
- itching
- pain

Many patients experience itching, reddening or swelling on or around the application site during the course of treatment. Some of these side effects could be a sign of an allergic reaction. If you experience open sores or other severe reactions at the locations you applied Veregen, stop treatment and call your doctor right away.

You may experience other side effects of Veregen Ointment, 15%, which are not mentioned here. Ask your doctor or pharmacist for more information.

Patients should be aware that new warts may develop during treatment as Veregen Ointment, 15% is not a cure.

How should I store Veregen Ointment, 15%?

- Store Veregen Ointment, 15% refrigerated or up to 77°F (25 °C).
- Do not freeze.
- Make sure the cap on the tube is tightly closed.
- Safely throw away Veregen Ointment, 15% tubes that are out of date or are empty.

Keep Veregen Ointment, 15% and all medicines out of the reach of children.

General advice about prescription medicines
Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use Veregen Ointment, 15% for a condition for which it was not prescribed. Do not give Veregen Ointment, 15% to other people, even if they have the same symptoms you have. It may harm them. Do not use Veregen Ointment, 15% after the expiration date on the tube.

This leaflet summarizes the most important information about Veregen Ointment, 15%. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about Veregen Ointment, 15% that is written for the doctor.

What are the ingredients in Veregen Ointment, 15%?

Active ingredient:
A defined green tea extract named Kunecatechins.

Inactive ingredients:
Isopropyl myristate, white petrolatum, cera alba (white wax), propylene glycol palmitostearate, and oleyl alcohol.

Veregen is a trademark of MediGene AG, D-82152 Planegg/Martinsried, Germany.

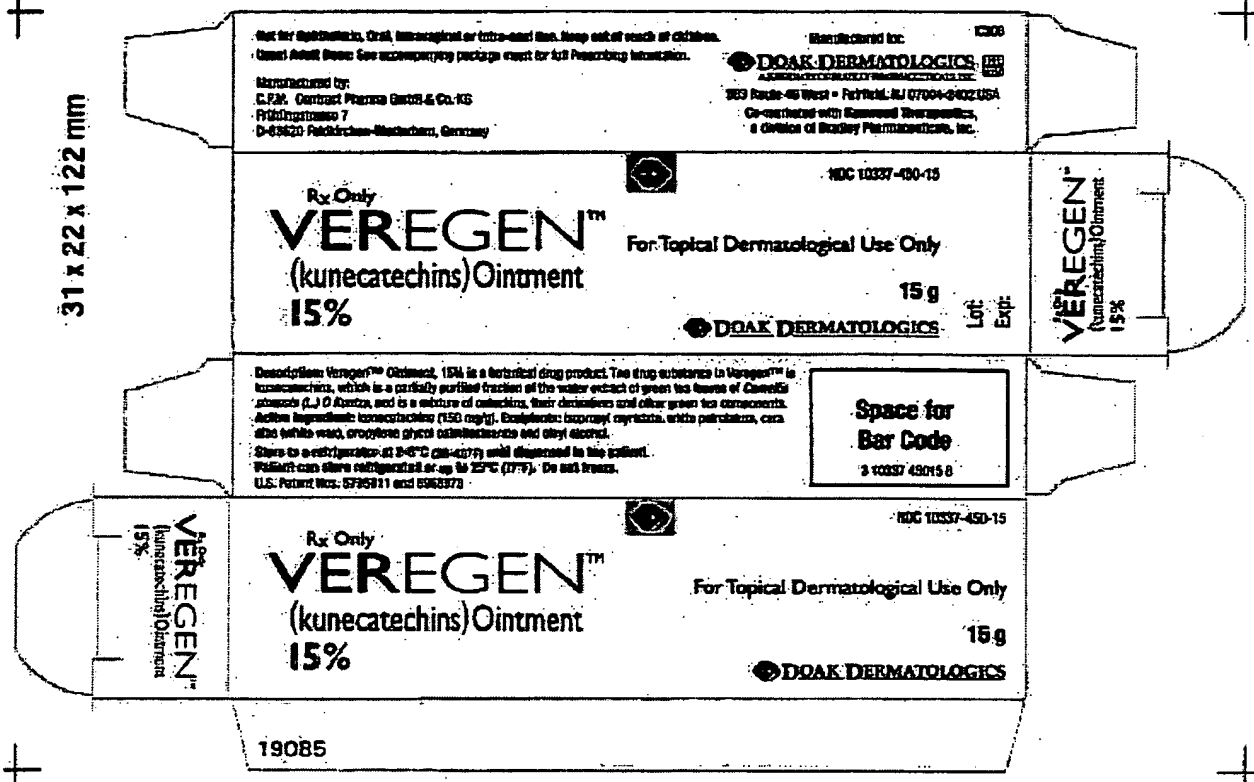
Manufactured by: C.P.M. Contract Pharma GmbH & Co. KG, Frühlingstrasse 7, D-83620 Feldkirchen-Westerham, Germany.

Manufactured for:

DOAK DERMATOLOGICS
A SUBSIDIARY OF BRADLEY PHARMACEUTICALS, INC.
383 Route 46 West
Fairfield, NJ 07004 2402 USA

Co-marketed with:

KENWOOD THERAPEUTICS
A DIVISION OF BRADLEY PHARMACEUTICALS, INC.


31 x 22 x 122 mm
Rx Only
VEREGEN™
(kunecatechins) Ointment
15%
For Topical Dermatological Use Only
15 g
DOAK DERMATOLOGICS
NDC 10337-450-15
Lot:
Exp:
Space for Bar Code
19085

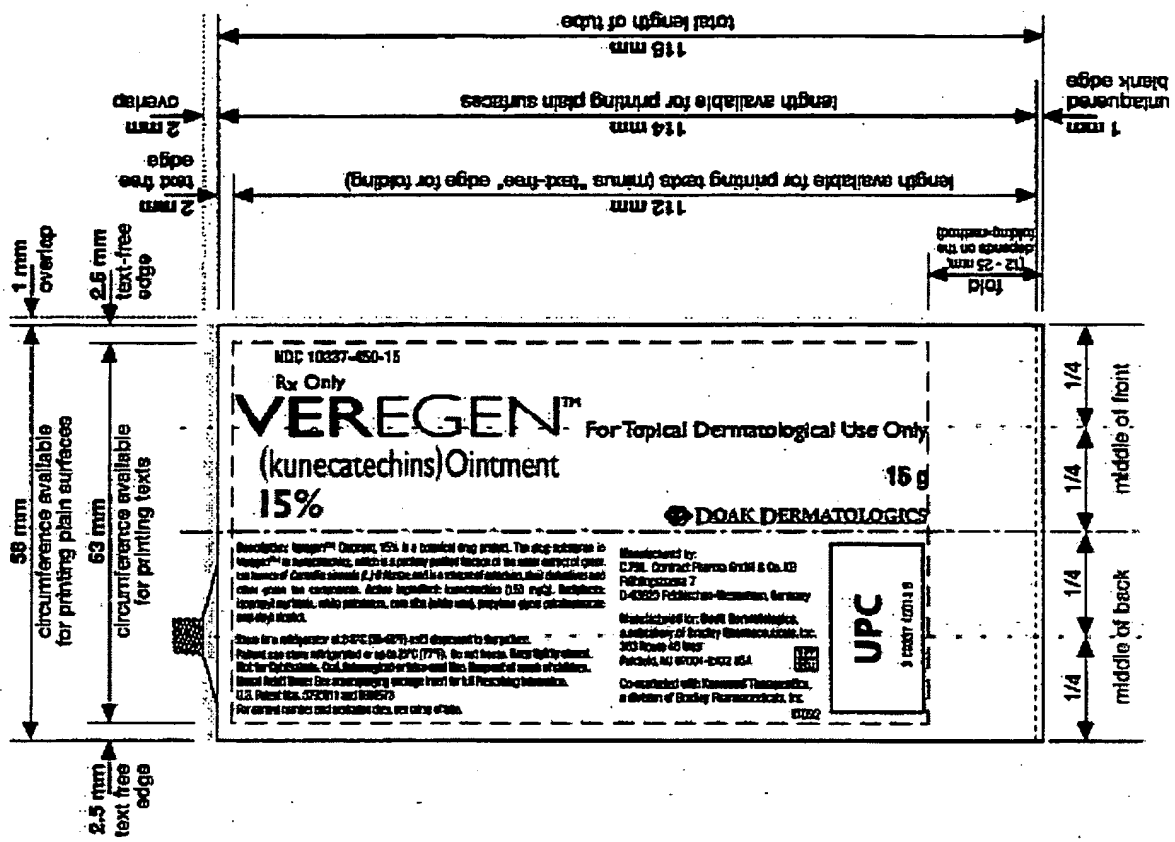

total length of tube
115 mm
length available for printing plain surfaces
114 mm
length available for printing texts (minus "text-free" edge for folding)
112 mm
unlaquered blank edge
1 mm
overlap
2 mm
text free edge
2.5 mm
text-free edge
fold
(12 - 25 mm, depends on the folding-method)
58 mm
circumference available for printing plain surfaces
63 mm
circumference available for printing texts
2.5 mm
text free edge
NDC 10337-450-15
Rx Only
VEREGEN™
For Topical Dermatological Use Only
(kunecatechins) Ointment
15%
15 g
DOAK DERMATOLOGICS
UPC
middle of front
middle of back
1/4
1/4
1/4
1/4

EXHIBIT 3
APPROVAL LETTER

NDA 21-902

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

Date: ~~October 31, 2006~~ November 1, 2006

Replacing due to message by Page & Millie

To: MediGene Inc.
Pam Larson, Sr. Manager, Regulatory Affairs
Mylcen Ignacio, Regulatory Affairs Assoc.
Phone: (858) 586-2246
Fax: (858) 586-2241

From: Millie Wright, Project Manager
Phone: (301) 976-2110
Fax: (301) 796-9895

This transmission includes 6 pages (including this page)

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DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-902

MediGene, Inc.
Attention: Pam Larson
Sr. Manager, Regulatory Affairs
10660 Scripps Ranch Blvd., Suite 200
San Diego, California 92131

Dear Ms. Larson

Please refer to your new drug application (NDA) dated September 23, 2005, received September 30, 2005, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Veregen™ (kunecatechins) Ointment, 15%.

We acknowledge receipt of your submissions dated December 9, 2005; January 6, 16 and 30; February 3, 16 (2), 22 and 28; March 2 and 6; April 17, 18 (2), 20 (2), 21 and 25; May 1, 3, 5, 18 and 26; June 2, 6 and 22; July 11 and 24; August 2, 9, 10, 14 (2), 16 and 18 (2); September 13, 14 (2) and 28; and October 4, 5, 6, 10, 13, 23, 24,26 (2), 27 and 30, 2006.

This new drug application provides for the use of Veregen™ (kunecatechins) Ointment, 15%, for the topical treatment of external genital and perianal warts (*Condylomata acuminata*) in immunocompetent patients 18 years and older.

We completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text, based on the agreed-upon drug specifications, provided in your October 4, 2006 amendment, and the raw material source and manufacturing process described in your NDA.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert and immediate container and carton labels). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-902.**" Approval of this submission by FDA is not required before the labeling is used.

Within 21 days of the date of this letter, submit content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html <http://www.fda.gov/oc/datacouncil/spl.html> , that is identical in content to the enclosed labeling text. Upon receipt and verification, we will transmit that version to the National Library of Medicine for public dissemination.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for this application because the number of pediatric patients is limited for this use.

We remind you of your postmarketing study commitment in your submission dated October 26, 2006. The commitment is listed below.

1. A phase 4 study comparing the pharmacokinetics of catechin following topical application of Veregen Ointment, 15%, with that obtained after oral administration of green tea solution. The two-arm study will be designed to enroll into one arm 20 evaluable patients ("completer") with external genital and perianal warts who will be treated 3 times daily for 7 days with Veregen Ointment, 15%, and into the second arm 20 evaluable healthy volunteers, who are to drink a green tea solution 3 times daily for 7 days. Blood samples for the analysis of catechin levels will be obtained prior to and at several sampling time points (over 12 hours) after oral intake of a green teal solution or topical application of Veregen Ointment, 15%, respectively, at Days 1 and 7. The study will be carried out with material from the final commercial source for API to be established in Japan and fulfilling the FDA-defined specifications for the botanical drug substance and drug product.

   Protocol to be submitted by July 2007.
   Study Start Date by January 2008
   Final Report Submission by January 2009.

Submit clinical protocols to your IND for this product. Under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Commitment Protocol**", "**Postmarketing Study Commitment Final Report**", or "**Postmarketing Study Commitment Correspondence.**"

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Dermatology and Dental Products and two copies of both the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

Please submit one market package of the drug product when it is available.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, call Millie Wright, Project Manager at (301) 796-2110.

Sincerely,

{See appended electronic signature page}
Daniel Shames, M.D.
Deputy Division Director (Acting)
Office of Drug Evaluations III
Center for Drug Evaluation and Research

Enclosure

VEREGEN™

(Kunecatechins)

Ointment, 15%

Rx Only

For Topical Dermatologic Use Only

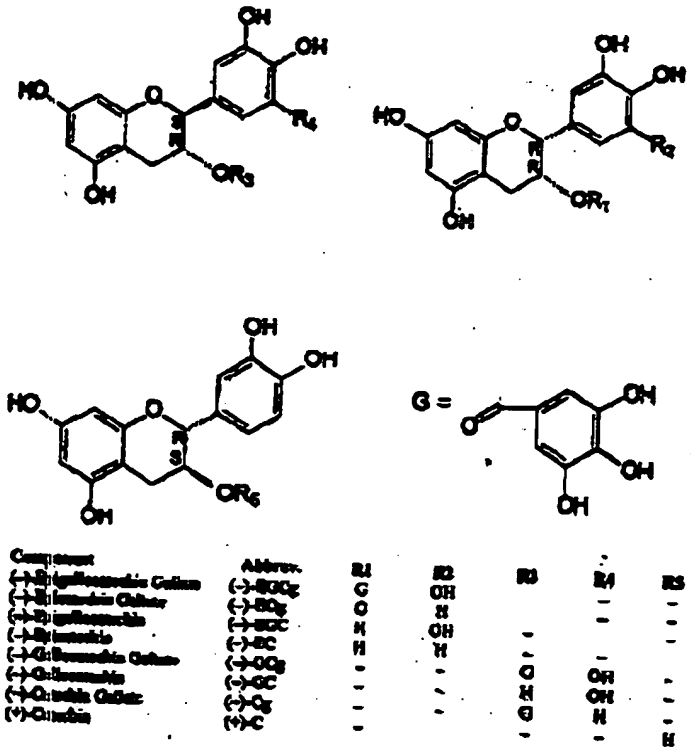
Not for Ophthalmic, Oral, Intravaginal, or Intra-anal Use

DESCRIPTION

Veregen™ is a botanical drug product for topical use. The drug substance in Veregen is Kunecatechins, which is a partially purified fraction of the water extract of green tea leaves from *Camellia sinensis (L.) O Kuntze*, and is a mixture of catechins and other green tea components. Catechins constitute 85 to 95% (by weight) of the total drug substance which includes more than 55% of Epigallocatechin gallate (EGCg), other catechin derivatives such as Epicatechin (EC), Epigallocatechin (EGC), Epicatechin gallate (ECg) and some additional minor catechin derivatives i.e. Gallocatechin gallate (GCg), Gallocatechin (GC), Catechin gallate (Cg), and Catechin (C). In addition to the known catechin components, it also contains gallic acid, caffeine, and theobromine which together constitute about 2.5% of the drug substance. The remaining amount of the drug substance contains undefined botanical constituents derived from green tea leaves.

The structural formulae of catechins are shown below.

General Structure of Catechins



Each gram of the ointment contains 150 mg of Kunecatechins in a water free ointment base consisting of isopropyl myristate, white petrolatum, cera alba (white wax), propylene glycol palmitostearate, and oleyl alcohol.

CLINICAL PHARMACOLOGY

Pharmacodynamics
The mode of action of Veregen™ Ointment, 15% involved in the clearance of genital and perianal warts is unknown. In vitro, Kunecatechins had anti-oxidative activity; the clinical significance of this finding is unknown.

Pharmacokinetics
The pharmacokinetics of topically applied Veregen Ointment has not been sufficiently characterized at this time. However, data suggest that systemic exposure to catechins after repeated topical application of Veregen Ointment 15% is likely to be less than observed after a single oral intake of 400ml green tea.

CLINICAL STUDIES

Two Phase 3 randomized, double-blind, vehicle-controlled studies were performed to investigate the safety and efficacy of Veregen™ Ointment in the treatment of immunocompetent patients 18 years of age and older with external genital and perianal warts. The subjects applied the ointment 3 times daily for up to 16 weeks or until complete clearance of all warts (baseline and new warts occurring during treatment).

Over both studies the median baseline wart area was 51 mm^2 (range 12 to 585 mm^2), and the median baseline number of warts was 6 (range 2 to 30).

The primary efficacy outcome measure was the response rate defined as the proportion of patients with complete clinical (visual) clearance of all external genital and perianal warts (baseline and new) by week 16, presented in Tables 1 and 2 for all randomized subjects dispensed medication.

Table 1: Efficacy by Region

	Complete Clearance
All Countries (includes the United States)	
Veregen™ 15% (*N* = 397)	213 (53.6%)
Vehicle (*N* = 207)	73 (35.3%)
United States	
Veregen™ 15% (*N* = 21)	5 (23.8%)
Vehicle (*N* = 9)	0 (0.0%)

Table 2. Efficacy by Gender

	Complete Clearance
Males	
Veregen™ 15% (*N* = 205)	97 (47.3%)
Vehicle (*N* = 118)	34 (28.8%)
Females	
Veregen™ 15% (*N* = 192)	116 (60.4%)
Vehicle (*N* = 89)	39 (43.8%)

Median time to complete wart clearance was 16 weeks and 10 weeks, respectively, in the two phase 3 clinical trials.

The incidence rate of recurrence of external genital and perianal warts after treatment in patients with complete clearance is unknown.

INDICATION AND USAGE

Veregen™ is indicated for the topical treatment of external genital and perianal warts (*Condylomata acuminata*) in immunocompetent patients 18 years and older.

CONTRAINDICATIONS

Veregen™ is contraindicated in individuals with a history of sensitivity reactions to any of the components of the ointment. In case of hypersensitivity, treatment should be discontinued.

WARNINGS

Veregen™ has not been evaluated for the treatment of urethral, intra-vaginal, cervical, rectal, or intra-anal human papilloma viral disease and should not be used for the treatment of these conditions.

PRECAUTIONS

General

Use of Veregen™ on open wounds should be avoided.
The safety and efficacy of Veregen™ in immunosuppressed patients have not been established.
Safety and efficacy have not been established for Veregen™ in the treatment of external genital and perianal warts beyond 16-weeks or for multiple treatment courses.
Patients should be advised to avoid exposure of the genital and perianal area to sun/UV-light as Veregen™ has not been tested under these circumstances.

Information for Patients

General Information

Patients using Veregen™ should receive the following information and instructions:

1. This medication is only to be used as directed by a physician. It is for external use only. Eye contact should be avoided as well as application into the vagina or anus.
2. It is not necessary to wash off Veregen™ prior to the next application. When the treatment area is washed or a bath is taken, the ointment should be applied afterwards.
3. It is common for patients to experience local skin reactions such as erythema, erosion, edema, itching, and burning at the site of application. Severe skin reactions can occur and should be promptly reported to the healthcare provider. Should severe local skin reaction occur, the ointment should be removed by washing the treatment area with mild soap and water and further doses held.
4. Sexual (genital, anal or oral) contact should be avoided while the ointment is on the skin, or the ointment should be washed off prior to these activities. Veregen™ may weaken condoms and vaginal diaphragms. Therefore the use in combination with Veregen™ is not recommended.
5. Female patients using tampons should insert the tampon before applying the ointment. If the tampon is changed while the ointment is on the skin, accidental application of the ointment into the vagina must be avoided.
6. Veregen™ may stain clothing and bedding.
7. Veregen™ is not a cure and new warts might develop during or after a course of therapy. If new warts develop during the 16 –week treatment period, these should also be treated with Veregen™.
8. The effect of Veregen™ on the transmission of genital/perianal warts is unknown.
9. Patients should be advised to avoid exposure of the genital and perianal area to sun/UV light as Veregen™ has not been tested under these circumstances.
10. The treatment area should not be bandaged or otherwise covered or wrapped as to be occlusive.
11. Uncircumcised males treating warts under the foreskin should retract the foreskin and clean the area daily.

Carcinogenesis, Mutagenesis, Impairment of Fertility
The Maximum Recommended Human Dose (MRHD) of Veregen™ Ointment, 15% was set at three times daily topical administration of 250 mg, 750 mg total, containing 112.5 mg Kunecatechins for the animal multiple of human exposure calculations presented in this labeling. Dose multiples were calculated based on the human equivalent dose (HED).

In an oral (gavage) carcinogenicity study, Kunecatechins was administered daily for 26 weeks to p53 transgenic mice at doses up to 500 mg/kg/day (22-fold MRHD). Treatment with Kunecatechins was not associated with an increased incidence of either neoplastic or non-neoplastic lesions in the organs and tissues examined. Veregen™ Ointment, 15% has not been evaluated in a dermal carcinogenicity study.

Kunecatechins was negative in the Ames test, in vivo rat micronucleus assay, UDS test, and transgenic mouse mutation assay, but positive in the mouse lymphoma mutation assay.

Daily vaginal administration of Veregen™ Ointment, 15% to rats from Day 4 before mating and throughout mating until Day 17 of gestation did not cause adverse effects on mating performance and fertility at doses up to 0.15 mL/rat/day. This dose corresponds to approximately 150 mg/rat/day (8-fold MRHD).

Pregnancy Category: C
Embryo-fetal development studies were conducted in rats and rabbits using intravaginal and systemic routes of administration, respectively. Oral administration of Kunecatechins during the period of organogenesis (gestational Days 6 to 15 in rats or 6 to 18 in rabbits) did not cause treatment related effects on embryo-fetal development or teratogenicity at doses of up to 1,000 mg/kg/day (86-fold MRHD in rats; 173-fold MRHD in rabbits).

In the presence of maternal toxicity (characterized by marked local irritation at the administration sites and decreased body weight and food consumption) in pregnant female rabbits, subcutaneous doses of 12 and 36 mg/kg/day of Kunecatechins during the period of organogenesis (gestational Days 6 to 19) resulted in corresponding influences on fetal development including reduced fetal body weights and delays in skeletal ossification. No treatment related effects on embryo-fetal development were noted at 4 mg/kg/day (0.7-fold MRHD). There was no evidence of teratogenic effects at any of the doses evaluated in this study.

A combined fertility / embryo-fetal development study using daily vaginal administration of Veregen™ Ointment, 15% to rats from Day 4 before mating and throughout mating until Day 17 of gestation did not show treatment-related effects on embryo-fetal development or teratogenicity at doses up to 0.15 mL/rat/day (8-fold MRHD).

A pre- and post-natal development study was conducted in rats using vaginal administration of Veregen™ Ointment, 15% at doses of 0.05, 0.10 and 0.15 mL/rat/day from Day 6 of gestation through parturition and lactation. The high and intermediate dose levels of 0.15 (8-fold MRHD) and 0.10 mL/rat/day resulted in an increased mortality of the F_0 dams, associated with indications of parturition complications. The high dose level of 0.15 mL/rat/day also resulted in an increased incidence of stillbirths. There were no other treatment-related effects on pre- and post-natal development, growth, reproduction and fertility at any dose tested.

There are no adequate and well-controlled studies in pregnant women. Veregen™ Ointment, 15% should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
It is not known whether topically applied Veregen™ is excreted in breast milk.

Pediatric Use
Safety and efficacy in pediatric patients have not been established.

Geriatric Use
Seven patients (1.4%), older than 65 years of age were treated with Veregen™ in clinical studies. This, however, is an insufficient number of subjects to determine whether they respond differently from younger subjects.

ADVERSE REACTIONS

ADVERSE EVENTS / LOCAL SKIN REACTIONS

In Phase 3 clinical trials, a total of 397 subjects received Veregen™ Ointment, 15% three times per day topical application for the treatment of external genital and perianal warts for up to 16 weeks.

Serious local adverse events of pain and inflammation were reported in two subjects (0.5%), both women.

In clinical trials, the incidence of local adverse events leading to discontinuation or dose interruption (reduction) was 5% (19/397). These included the following events: application site reactions (local pain, erythema, vesicles, skin erosion/ulceration), phimosis, inguinal lymphadenitis, urethral meatal stenosis, dysuria, genital herpes simples, vulvitis, hypersensitivity, pruritus, pyodermitis, skin ulcer, erosions in the urethral meatus, and superinfection of warts and ulcers.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect rates observed in practice.

Local and regional reactions (includes adenophathy) occurring at >1% in the treated group are presented in Table 3.

Table 3: Local and Regional Adverse Reactions During Treatment (% Subjects)

	Veregen *(N=397)*	Vehicle *(N=207)*
Erythema	70	32
Pruritus	69	45
Burning	67	31
Pain/discomfort	56	14
Erosion/Ulceration	49	10
Edema	45	11
Induration	35	11
Rash vesicular	20	6
Regional Lymphadenitis	3	1
Desquamation	5	<1
Discharge	3	<1
Bleeding	2	<1
Reaction	2	0
Scar	1	0
Irritation	1	0
Rash	1	0

A total of 266/397 (67%) of subjects in the Veregen, 15% group had either a moderate or a severe reaction that was considered probably related and of these 120 (30%) subjects had a severe reaction. Severe reactions occurred in 37% (71/192) of women and in 24% (49/205) of men. The percentage of subjects with at least one severe, related adverse event was 26% (86/328) for subjects with genital warts only, 42% (19/45) in subjects with both genital and perianal warts and 48% (11/23) of subjects with perianal warts only.

Phimosis occurred in 3% of uncircumcised male subjects (5/174) treated with Veregen and in 1% (1/99) in vehicle.

The maximum mean severity of erythema, erosion, edema and induration was observed by week 2 of treatment.

Less common local adverse events included urethritis, perianal infection, pigmentation changes, dryness, eczema, hyperesthesia, necrosis, papules, and discoloration. Other less common adverse events included cervical dysplasia, pelvic pain, cutaneous facial rash and staphylococcemia.

In a dermal sensitization study of Veregen ointment in healthy volunteers, hypersensitivity (type IV) was observed in 5 out of 209 subjects (2.4%) under occlusive conditions.

OVERDOSAGE

Overdosage with Veregen™ has not been reported.

DOSAGE AND ADMINISTRATION
Veregen™ Ointment, 15% is to be applied three times per day to all external genital and perianal warts.

It is recommended to wash the hands before and after application of Veregen™ About an 0.5 cm strand of the Veregen™ Ointment, 15% should be applied to each wart using the finger(s), dabbing it on to ensure complete coverage and leaving a thin layer of the ointment on the warts.

It is not necessary to wash off the ointment from the treated area prior to the next application.

Treatment with Veregen™ should be continued until complete clearance of all warts, however no longer than 16 weeks.

Local skin reactions (e.g. erythema) at the treatment site are frequent. Nevertheless, treatment should be continued when the severity of the local skin reaction is acceptable.

HOW SUPPLIED
Veregen™ ointment, 15% is a brown ointment and is supplied in aluminium tubes containing 15 gram ointment per tube.

Storage Conditions
Prior to dispensing to the patient, store refrigerated 2^0C to 8^0C (36^0F to 46^0F). After dispensing, store refrigerated or up to 25°C (77°F).
Do not freeze.
Keep out of reach of children

NDC # 10337-450-15

The VEREGEN trademark is used by Bradley Pharmaceuticals, Inc. under license from MediGene AG."

Manufactured by:
C.P.M. Contract Pharma GmbH & Co. KG
Frühlingstrasse 7
D-83620 Feldkirchen-Westerham
Germany

Manufactured for:

DOAK DERMATOLOGICS
A SUBSIDIARY OF BRADLEY PHARMACEUTICALS, INC.

383 Route 46 West
Fairfield, NJ 07004-2402 USA
Co-marketed with Kenwood Therapeutics, a division of Bradley Pharmaceuticals, Inc.

PATIENT INFORMATION

Veregen
(Kunecatechins)
Ointment, 15%

Rx Only

Read this leaflet carefully before you start using Veregen Ointment, 15% and each time you refill your prescription. There may be new information. This information does not take the place of your doctor's advice. If you have any questions about Veregen Ointment, 15% or your condition ask your doctor or pharmacist. Only your doctor can prescribe Veregen and determine if it is right for you.

What is Veregen Ointment, 15%?
Veregen Ointment, 15% is a medicine for skin use only (topical) for the treatment of warts on the outside of the genitals and around the outside of the anus caused by a virus known as the human papilloma virus (HPV) in adults. It is not a treatment for the HPV infection in the vagina, cervix, or inside the anus. Your doctor may recommend examination and screening tests (such as a Pap smear) to look for signs of the HPV infection in these areas.

Who should not use Veregen Ointment, 15%?
Do not use Veregen Ointment, 15% if you **are allergic** to an ingredient in Veregen Ointment, 15%. **The list of ingredients is at the end of this leaflet.**

What should I tell my doctor before taking Veregen Ointment, 15%?
Tell your doctor about all your health conditions and all the medicines you take including prescription, over-the-counter medicine, vitamins, supplements, and herbals. Be sure to tell your doctor if you are:

- **pregnant or planning to become pregnant,** as it is not known if Veregen Ointment, 15% can harm your unborn baby. Your doctor will determine whether the benefit outweighs the risk.
- **breastfeeding,** as it is not known if Veregen Ointment, 15% can pass into your milk and if it can harm your baby.
- **using any other type of skin product or have open wounds on the area to be treated.** Veregen Ointment, 15% should not be used until your skin has healed from other treatments applied to the same area.
- **immunocompromised**. This means that your immune system cannot fight infections as well as it should.

How should I use Veregen Ointment, 15%?

- Use Veregen Ointment, 15% only on the area affected **exactly** as prescribed by your doctor.

- **Wash your hands before and after application of Veregen Ointment, 15%.** A small amount of the ointment should be applied to all wart using your finger(s), dabbing it on to ensure complete coverage and leaving a thin layer of the ointment on the warts as directed by your doctor.

- **Apply Veregen Ointment, 15% three times per day —in the morning, at noontime and in the evening.**

- Do not wash off the ointment from the treated area before the next application. When you wash the treatment area or bathe, apply the ointment afterwards.

- Treatment with Veregen Ointment, 15% should be continued until complete clearance of all warts, however **no longer than 16 weeks.** If your warts do not go away, or if they come back after treatment call your doctor.

- Veregen Ointment, 15% is not a cure for warts on your genitals or around your anus with certainty. New warts may develop during or after treatment, and may need treatment.

What Should I Avoid While Using Veregen Ointment, 15%?

- Do not apply Veregen Ointment, 15% on open wounds or into the vagina or into the anus.

- Genital warts are a sexually transmitted disease, and you may infect your partner.

- Avoid sexual contact (genital, anal or oral) when Veregen Ointment, 15% is on your genital or perianal skin. If you do choose to have sexual contact, you must wash off the ointment carefully before having protected sexual contact as the ointment may weaken condoms and vaginal diaphragms. Talk to your doctor about safe sex practices.

- Avoid contact with your eyes, nostrils and mouth while ointment is on your finger(s).

- Women using tampons: insert the tampon before applying the ointment. If you need to change your tampon while the ointment is on your skin, avoid getting the ointment into the vagina.

- Uncircumcised men treating warts under the foreskin should retract the foreskin and clean the area daily.

- Do not expose the genital area treated with Veregen Ointment, 15% to sunlight, sunlamps or tanning beds.

- Do not cover the treated area. Loose-fitting undergarments can be worn after applying Veregen Ointment, 15%.

- Veregen Ointment, 15% may stain your light colored clothes and bedding. It is recommended to wear darker colored undergarments while using Veregen Ointment, 15%.

What are the possible side effects of Veregen Ointment, 15%?
The most common side effects with Veregen Ointment, 15% are local skin and application site reactions including:

- redness
- swelling
- sores or blisters
- burning
- itching
- pain

Many patients experience itching, reddening or swelling on or around the application site during the course of treatment. Some of these side effects could be a sign of an allergic reaction. If you experience open sores or other severe reactions at the locations you applied Veregen, stop treatment and call your doctor right away.

You may experience other side effects of Veregen Ointment, 15%, which are not mentioned here. Ask your doctor or pharmacist for more information.

Patients should be aware that new warts may develop during treatment as Veregen Ointment, 15% is not a cure.

How should I store Veregen Ointment, 15%?

- Store Veregen Ointment, 15% refrigerated or up to 77°F (25 °C).
- Do not freeze.
- Make sure the cap on the tube is tightly closed.
- Safely throw away Veregen Ointment, 15% tubes that are out of date or are empty.

Keep Veregen Ointment, 15% and all medicines out of the reach of children.

General advice about prescription medicines
Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use Veregen Ointment, 15% for a condition for which it was not prescribed. Do not give Veregen Ointment, 15% to other people, even if they have the same symptoms you have. It may harm them. Do not use Veregen Ointment, 15% after the expiration date on the tube.

This leaflet summarizes the most important information about Veregen Ointment, 15%. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about Veregen Ointment, 15% that is written for the doctor.

What are the ingredients in Veregen Ointment, 15%?

Active ingredient:
A defined green tea extract named Kunecatechins.

Inactive ingredients:
Isopropyl myristate, white petrolatum, cera alba (white wax), propylene glycol palmitostearate, and oleyl alcohol.

Veregen is a trademark of MediGene AG, D-82152 Planegg/Martinsried, Germany.

Manufactured by: C.P.M. Contract Pharma GmbH & Co. KG, Frühlingstrasse 7, D-83620 Feldkirchen-Westerham, Germany.

Manufactured for:

DOAK DERMATOLOGICS
A SUBSIDIARY OF BRADLEY PHARMACEUTICALS, INC.
383 Route 46 West
Fairfield, NJ 07004 2402 USA

Co-marketed with:

KENWOOD THERAPEUTICS
A DIVISION OF BRADLEY PHARMACEUTICALS, INC.

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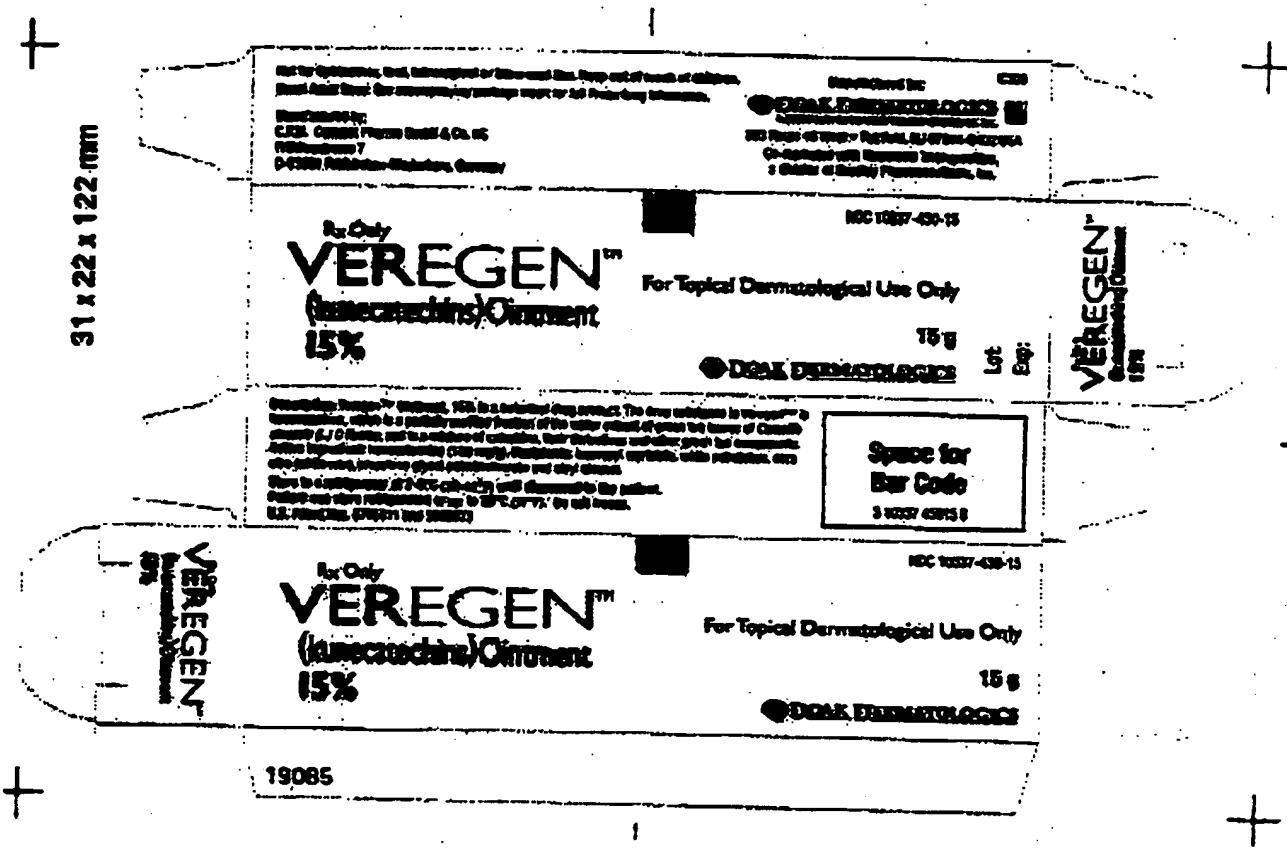

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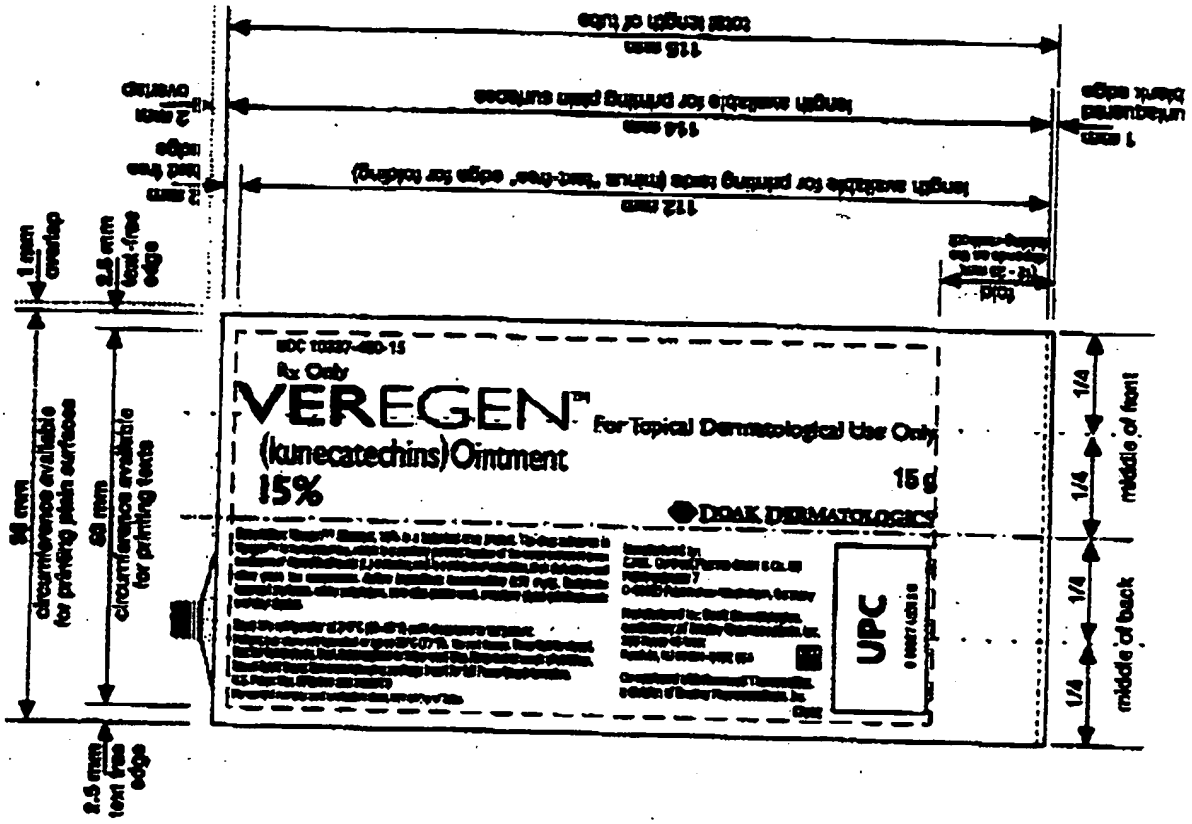

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/s/

Daniel A. Shames
10/31/2006 11:12:51 AM

EXHIBIT 4
RECORDED ASSIGNMENT

10/96FH:GL&C

S. Attorney Docket _____

ASSIGNMENT

In consideration of value received, I, having a residence and post office address as stated below next to my name, the sole inventor (if only one name is listed below) or a joint inventor (if plural names are listed below) of an invention described in an application for United States patent entitled:

COMPOSITION FOR TREATING CONDYLOMA ACUMINATA

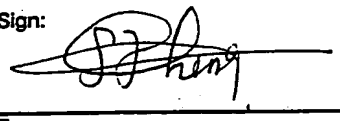
sell and assign to 1) Cancer Institute (Hospital), Chinese Academy of Medical Sciences ;
and 2) Mitsui Norin Co., Ltd.
a corporation of 1) People's Republic of China; and 2) Japan
having a business address at
1) Panjiayuan No. 17, Chaoyang District, Beijing 100021, People's Republic of China
2) 1-20, Nihonbashimuromachi 3-chome, Chuo-ku, Tokyo, Japan
its successors, assigns or nominees, hereinafter referred to as "Assignee", my entire right, title and interest in and to said invention as disclosed, shown and described in said application for United States patent executed concurrently herewith;

and in and to all applications for patent and patents for said invention, in all countries of the world, including all divisions, reissues, continuations, substitutions and extensions thereof and all rights arising under or pursuant to any and all international agreements, treaties or laws relating to the protection of industrial property, including rights of priority, resulting from the filing of any of said applications; and I authorize and request any official whose duty it is to issue patents, to issue any patent on said invention or resulting therefrom to said Assignee, and I agree that on request and without further consideration, but at the expense of said Assignee, I will communicate to said Assignee or its representatives all facts known to me respecting said invention and testify in any legal proceeding, sign all lawful papers, execute all divisional, continuing, reissue, or other applications, make all rightful oaths and declarations, and generally do everything possible to aid said Assignee to obtain and enforce proper patent protection for said invention in all countries.

I hereby grant to any attorney member of the following law firm the power to insert on this Assignment the Serial Number and filing date of said application when known.

SERIAL NO.: FILING DATE:

Frishauf, Holtz, Goodman, Langer & Chick, P.C., 767 Third Avenue - 25th Floor, New York, N.Y. 10017-2023.

INVENTOR: SIGNATURE	DATE	ADDRESS
Sign: 	Date: 17, March 1997	Address: c/o Cancer Institute (Hospital), Chinese Academy of Medical Sciences Panjiayuan No. 17, Chaoyang District, Beijing 100021, People's Republic of China
Type: Shu Jun Cheng	Witness:	
Sign: D.C. Wang	Date: 1997.3.19.	Address: c/o Cancer Institute (Hospital), Chinese Academy of Medical Sciences Panjiayuan No. 17, Chaoyang District, Beijing 100021, People's Republic of China
Type: De Chang Wang	Witness:	
Sign: Y. Hara	Date: March 28, 1997	Address: 2-7, Minamisurugadai 2-chome, Fujieda-shi, Shizuoka-ken, Japan
Type: Yukihiko Hara	Witness:	

NOTES: MUST BE DATED. WITNESS DESIRABLE. LEGALIZATION NOT REQUIRED.

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767 Third Avenue - 25th Floor, New York, N.Y. 10017-2023
Tel. No.: (212) 319-4900 Fax No.: (212) 319-5101

EXHIBIT 5
PATENT

US005795911A

United States Patent [19]

Cheng et al.

[11] Patent Number: 5,795,911

[45] Date of Patent: Aug. 18, 1998

[54] **COMPOSITION FOR TREATING *CONDYLOMA ACUMINATA***

[75] Inventors: **Shu Jun Cheng**; **De Chang Wang**, both of Beijing, China; **Yukihiko Hara**, Fujieda, Japan

[73] Assignees: **Cancer Institute (Hospital), Chinese Academy of Medical Sciences**, Beijing, China; **Mitsui Norin Co., Ltd.**, Tokyo, Japan

[21] Appl. No.: **835,920**

[22] Filed: **Apr. 10, 1997**

[30] **Foreign Application Priority Data**

Nov. 18, 1996 [JP] Japan 8-321195

[51] **Int. Cl.**^{6} **A61K 31/35**

[52] **U.S. Cl.** **514/456**

[58] **Field of Search** 514/456

[56] **References Cited**

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Primary Examiner—Raymond Henley, III

Attorney, Agent, or Firm—Frishauf, Holtz, Goodman, Langer & Chick, P.C.

[57] **ABSTRACT**

A composition for a treatment of HPV-infected Condyloma acuminata which comprises containing tea catechin as a main component. This medication has no danger of side-effects and may be easily applied to or inserted in the infected area by the patient themselves.

15 Claims, No Drawings

COMPOSITION FOR TREATING *CONDYLOMA ACUMINATA*

FIELD OF THE INVENTION

The present invention relates to a composition for treating Condyloma acuminata, or more specifically to a composition for treating Condyloma acuminata caused by human papilliomavirus, containing treating catechin as a main component.

BACKGROUND OF THE INVENTION

Condyloma acuminata is a wart detectable on the skin or mucous membrane of the genital organs of men and women, and is caused by human papilloma virus (HPV). The site of infection in men is the balanic area, coronary sulcus, foreskin, anal area, urethral meatus; and in women is the vagina, labium, anal area and urethral orifice. Clinical symptoms appear from 1–6 months, on average 3 months after infection, but usually symptoms are not noticed by the patient. This wart shows distinctive papillary or cockscomb-like tumors and has a tendency to accumulate and multiply and is usually red or reddish brown in colour. Detection of HPV in condyloma acuminata is by a method of taking tissue or a smear from the infected area and determining the DNA of the virus.

According to this method the detection rate is almost 100%. Types HPV6 and 11 of the virus are the ones most commonly detected and because HPV16 has been detected in malignant squamous cell carcinoma from cancer of the penis, cancer of the cervix and Condyloma acuminata, there is a strong possibility that HPV16 is related to the malignancy of Condyloma acuminata.

Means for a treatment of Condyloma acuminata caused by human papilloma virus which have been tried at present are by physical means such as surgical excision, electrocauterization, cryosurgery, laser therapy etc. and medication such as applications of Podophyllin, 5-Fluorouracil, Bleomycin, Interferon etc. are presently available. However surgical treatment is distressing for the patient, considering the site of infection, and with topical applications there is the concern of side-effects. Because of this no conclusive treatment is presently available.

Condyloma acuminata has a high rate of recurrence, and a complete cure is difficult unless treated constantly. Because of this a treatment which has a high degree of safety and is convenient is strongly desired.

SUMMARY OF THE INVENTION

Thus for the treatment of condyloma acuminata caused by human papillomavirus, desired is a treatment which is easy for the patient to take, for example a medication which can be applied to the affected area by the patient themselves showing good results in a relatively short period of use and having no side-effects.

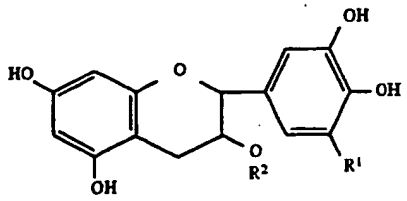
DESCRIPTION OF THE INVENTION

We, the present inventors looked for a natural substance which has no side-effects, may be safely applied for a long period of time by the patient themselves and is notably effective; and after extensive testing we discovered that catechin, a component of tea which is an everyday beverage, is effective and thus the present invention was developed.

Thus the present invention relates to a composition for a treatment of Condyloma acuminata caused by human papillomavirus containing tea catechin as a main component.

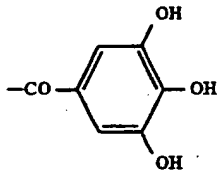
DETAILED DESCRIPTION OF THE INVENTION

The tea catechin of the present invention is shown below in the general formula 1



I

wherein R^1 represents H or OH and R^2 represents H or



The tea catechins are more specifically, epicatechin, epicatechin gallate, epigallocatechin gallate, gallocatechin etc. (including derivatives thereof). These catechins can be used singly or two or more may be mixed together. Out of these it is particularly desirable to have (−)-epigallocatechin gallate as a main component. For example: Polyphenon 100™ (produced by Mitsui Norin Co.; Composition: (+)-gallocatechin 1.44%, (−)-epicatechin 5.81%, (−)-epigallocatechin 17.57%, (−)-epicatechin gallate 12.51%, (−)-epigallocatechin gallate 53.90%); or Polyphenon E™ (produced by Mitsui Norin Co.; Composition: (−)-epicatechin 10.8%, (−)-epigallocatechin 9.2%, (−)-epicatechin gallate 6.5%, (−)-epigallocatechin gallate 54.8%, (−)-gallocatechin gallate 4.0%).

The treatment for Condyloma acuminata of the present invention could be used for example in the form of ointment such as a cream, jelly, emulsion; or in the form of suppository such as a capsule, and usually the tea catechin component is combined with an excipient, extending agent, emulsifier, dispersing agent etc. Vaseline is suitable as a base for the ointment. For the ointment the content of tea catechin should be between 5–20% by weight, preferably between 12–18% by weight, more preferably 15% by weight. In the case of suppository the content of tea catechin should be 100–500 mg/capsule, preferably 200–300 mg/capsule, or more preferably 250 mg/capsule.

A typical usage example for the ointment is to apply directly to the infected area of the external genital organs or vagina, a vaseline cream containing 5–% by weight catechin, from once to several times everyday for a period of 1–2 months. A typical usage example for the suppository in the case where for example the infected area is the cervix or the vagina is to insert a capsule containing 100–500 mg tea catechin, from once to several times everyday for a period of 1–2 months.

There is no danger of side-effects from the treatment for condyloma acuminata with the composition of the present invention having tea catechin as the main component thereof since the main component is a natural substance derived from tea which is commonly consumed regularly, and it may be taken for long periods of time. Moreover this medication may be easily applied to or inserted in the infected area by the patient themselves. The composition of the present invention for a treatment of condyloma acuminata has a very high potential for practical use.

Another aspect of the invention is a method of applying an effective treating human papilloma virus-infected Condyloma acuminata amount of tea catechin to an infected area of a patient to treat human papilloma virus-infected Condyloma acuminata.

EXAMPLES

The present invention will be explained in more detail with reference to the following examples which are in no way meant to limit the scope of the invention.

Test Example 1

An ointment consisting essentially of a vaseline based vaginal lubricant containing, as the main component, tea catechin (Trade name: Polyphenon 100, produced by Mitsui Norin Co. Ltd., its main component: (−)-epigallocatechin gallate) was applied to the cervix of healthy mice (50 mice in a group) in catechin dosages of 8 mg, 15 mg, or 38 mg for a period of 7 consecutive days. After this time pathological and histological examinations were carried out and it was determined that except for a mild inflammatory reaction in the cervix of the mice of the 38 mg dose group no toxic effect was observed.

Example 1

Clinical tests of the present invention were carried out at the Cancer Institute, Chinese Academy of Medical Sciences in Beijing with a group of 15 women who had been diagnosed with HPV-infected condyloma acuminata. All patients were confirmed to have condyloma in the vulva (external genital organs), vagina and/or cervix according to clinical examination, cytologic, colposcopic and pathologic tests. Two of the fifteen patients were confirmed to be infected in two areas. Warts were from 0.2 to 2 cm in diameter.

Tests were carried out on these 15 patients using an ointment containing 10–15% of vaseline based vaginal lubricant and 5–20% of tea catechin (Trade name: Polyphenon 100, produced by Mitsui Norin Co. Ltd., crude catechin content is about 90% and its main component is (−)-epigallocatechin gallate) or using a suppository containing 100–500 mg/capsule of the above tea catechin. Applying the ointment to the external genital organs and applying the suppository to the vagina and cervix, the treatments of the present invention were used continuously once a day for about two months.

During the period of treatment examinations and colposcopic tests of the infected areas were carried out. Results obtained are shown in Table 1. As shown in the table, when the infected area completely disappeared it was judged to be cured, when 50% or more disappeared it was judged to be improved and when less than 50% or nothing disappeared it was judged there was no effect.

TABLE 1

Infected Area	No. of Patients	Cured	Improved	No Effect
External genital organs	9	4	3	2
Vagina	6	0	1	5
Cervix	2	1	0	1
Total	17	5	4	8
(%)		(29.4)	(23.5)	(47.1)

As is evident from the table, 7 cases out of 9 (77.8%) of condyloma acuminata of the external genital organ showed a clear effect (being either cured or improved). In one case of the cervical infection the tumor completely disappeared, thus cured. During this period, apart from some patients who experienced slight pain or inflammation in the infected area and a few other patients who felt some itching, there were no obvious side-effects observed.

Example 2

The clinical tests at the Cancer Institute, Chinese Academy of Medical Sciences in Beijing were conducted in the same manner as in Example 1 with a group of 33 female patients diagnosed with HPV-infected condyloma acuminata. In this group, 8 of the patients were infected in two areas. Results are shown in Table 2. As is evident from the table, 92% of condyloma acuminata of the external genital organs and 70% of the vaginal condyloma acuminata was cured or improved, and in the case of the cervical condyloma acuminata, all cases were cured. 25 cases out of 41 cases showed the result as cured and the curing ratio was 61%.

TABLE 2

Infected Area	No. of Patients	Cured	Improved	No Effect
External genital organs	26	18	6	2
Vagina	10	2	5	3
Cervix	5	5	0	0
Total	41	25	11	5
(%)		(61.0)	(26.8)	(12.2)

Example 3

The clinical test at the Cancer Institute, Chinese Academy of Medical Sciences in Beijing was conducted in the same manner as in Example 1 with a group of 22 female patients diagnosed with HPV-infected condyloma acuminata. Results are shown in Table 3. As is evident from the table, out of 16 cases of condyloma acuminata of the external genital organs 7 were cured and 6 improved; a total of 13 (81.3%) being effected. In the case of condyloma acuminata of the vagina, out of 6 cases 3 were cured and 2 were improved; a total of 83.3% was confirmed to be effected.

TABLE 3

Infected Area	No. of Patients	Cured	Improved	No Effect
External genital organs	16	7	6	3
Vagina	6	3	2	1
Total	22	10	8	4
(%)		(45.5)	(36.4)	(18.2)

The entire disclosure of Japanese Patent Application No. 8-321195 filed on Nov. 18, 1996 including specification, claims and summary are incorporated herein by reference in its entirety.

What is claimed is:

1. A method of treating Condyloma acuminata caused by human papillomavirus, comprising applying to an infected area on a human a composition which comprises a tea catechin as a main component in an amount effective for treating Condyloma acuminata.

2. The method according to claim 1, wherein the composition is in the form of an ointment or a suppository.

3. The method according to claim 1, wherein said composition is in the form of an ointment having 5–20% by weight of tea catechin.

4. The method according to claim 1, wherein said composition is in the form of a suppository having 100–500 mg of the tea catechin in a capsule.

5. The method according to claim 1, wherein said tea catechin comprises (−)-epigallocatechin.

6. The method according to claim 3, wherein the tea catechin is in an amount of 12–18% by weight.

7. The method according to claim 4, wherein the tea catechin is in an amount of 15% by weight.

8. The method according to claim 3, wherein the capsule contains 200–300 mg of the tea catechin.

9. The method according to claim 4, wherein the capsule contains 250 mg of the tea catechin.

10. The method according to claim 3, wherein the ointment contains vaseline as a base to form a cream.

11. The method according to claim 3, wherein the ointment is applied to external genital organs.

12. The method according to claim 4, wherein the suppository is applied to the vagina of a human.

13. The method according to claim 1, wherein the infected area is the vagina.

14. The method according to claim 1, wherein the infected area is an external genital organ.

15. The method according to claim 1, wherein the infected area is the cervix.

* * * * *

EXHIBIT 6
CERTIFICATE OF CORRECTION

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,795,911
DATED : August 18, 1998
INVENTOR(S) : CHENG et al

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 5, line 8 (Claim 7): delete "4" and insert --3--.

Column 5, line 10 (Claim 8): delete "3" and insert --4--.

Signed and Sealed this

Twenty-third Day of November, 1999

Attest:

Q. TODD DICKINSON

Attesting Officer

Acting Commissioner of Patents and Trademarks

EXHIBITS 7A and 7B
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The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 11, "STAT" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 11, "STAT" below. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(h).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITEM NBR	PATENT NUMBER	FEE CDE	FEE AMT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	5,795,911	183	850	----	08/835,920	08/18/98	04/10/97	04	NO	PAID

ITM NBR	ATTY DKT NUMBER
1	970232/HG

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PATENT NUMBER	FEE AMT	SUR CHARGE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	STAT	ATTY DKT NUMBER
5,795,911	$2,300.00	$0.00	08/835,920	08/18/98	04/10/97	08	NO	PAID	970232/HG

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EXHIBIT 8
IND SUBMISSION LETTER

5162 DUKE STREET, SUITE 501, HALIFAX, NS B3J 1N7 CANADA
3920 GOLDFINCH STREET, SAN DIEGO, CA 92103 USA
TEL/FAX (619) 298-4279, PAUL@EPITOMEPHARM.COM

7 July, 1998

Dr. Roy Blay
Project Manager
Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

Dear Dr. Blay:

Epitome Pharmaceuticals, Ltd. hereby submits an Investigational New Drug application for Polyphenon ointment for the treatment of external genital warts.

I enclose an original, as marked, and two copies. I also enclose copies of all the literature cited in the IND as separate binders, for the convenience of the reviewers.

Please call me with any questions. I will be travelling until 19th July, but I will be receiving my messages and I will respond as soon as possible. I look forward to hearing from you soon.

Sincerely yours,

Paul T. Wegener

PTW/ccl

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

INVESTIGATIONAL NEW DRUG APPLICATION (IND)

(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)

Form Approved: OMB No. 0910-0014.
Expiration Date: December 31, 1999
See OMB Statement on Reverse.

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).

1. NAME OF SPONSOR: Epitome Pharmaceuticals Ltd

2. DATE OF SUBMISSION: 6/25/98

3. ADDRESS *(Number, Street, City, State and Zip Code)*: 3920 Goldfinch St, San Diego, CA 92103

4. TELEPHONE NUMBER *(Include Area Code)*: 619 298-4279

5. NAME(S) OF DRUG *(Include all available names: Trade, Generic, Chemical, Code)*: Polyphenon ointment "Wart Heal"

6. IND NUMBER *(If previously assigned)*: ~~000~~

7. INDICATION(S) *(Covered by this submission)*: external genital warts

8. PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED:
☐ PHASE 1 ☒ PHASE 2 ☐ PHASE 3 ☐ OTHER _____ *(Specify)*

9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, DRUG MASTER FILES *(21 CFR Part 314.420)*, AND PRODUCT LICENSE APPLICATIONS (21 CFR Part 601) REFERRED TO IN THIS APPLICATION.

none

10. *IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.*

SERIAL NUMBER: 000

11 THIS SUBMISSION CONTAINS THE FOLLOWING: *(Check all that apply)*

☒ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND)
☐ RESPONSE TO CLINICAL HOLD

PROTOCOL AMENDMENT(S):	INFORMATION AMENDMENT(S):	IND SAFETY REPORT(S):
☐ NEW PROTOCOL	☐ CHEMISTRY/MICROBIOLOGY	☐ INITIAL WRITTEN REPORT
☐ CHANGE IN PROTOCOL	☐ PHARMACOLOGY/TOXICOLOGY	☐ FOLLOW-UP TO A WRITTEN REPORT
☐ NEW INVESTIGATOR	☐ CLINICAL	

☐ RESPONSE TO FDA REQUEST FOR INFORMATION
☐ ANNUAL REPORT
☐ GENERAL CORRESPONDENCE
☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED
☐ OTHER _____ *(Specify)*

CHECK ONLY IF APPLICABLE

JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.

☐ TREATMENT IND 21 CFR 312.35(b) ☐ TREATMENT PROTOCOL 21 CFR 312.35(a) ☐ CHARGE REQUEST/NOTIFICATION 21 CFR312.7(d)

FOR FDA USE ONLY

CDR/DBIND/OGD RECEIPT STAMP	DDR RECEIPT STAMP	DIVISION ASSIGNMENT:
		IND NUMBER ASSIGNED:

12. **CONTENTS OF APPLICATION**

This application contains the following items: *(Check all that apply)*

- [X] 1. Form FDA 1571 *[21 CFR 312.23(a)(1)]*
- [X] 2. Table of Contents *[21 CFR 312.23(a)(2)]*
- [X] 3. Introductory statement *[21 CFR 312.23(a)(3)]*
- [X] 4. General Investigational plan *[21 CFR 312.23(a)(3)]*
- [X] 5. Investigator's brochure *[21 CFR 312.23(a)(5)]*
- [X] 6. Protocol(s) *[21 CFR 312.23(a)(6)]*
  - [X] a. Study protocol(s) *[21 CFR 312.23(a)(6)]*
  - [X] b. Investigator data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - [X] c. Facilities data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - [X] d. Institutional Review Board data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
- [X] 7. Chemistry, manufacturing, and control data *[21 CFR 312.23(a)(7)]*
  - [X] Environmental assessment or claim for exclusion *[21 CFR 312.23(a)(7)(iv)(e)]*
- [X] 8. Pharmacology and toxicology data *[21 CFR 312.23(a)(8)]*
- [X] 9. Previous human experience *[21 CFR 312.23(a)(9)]*
- [X] 10. Additional information *[21 CFR 312.23(a)(10)]*

13. IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION? [ ] YES [X] NO

IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION? [ ] YES [X] NO

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED.

14. NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS

Paul T. Wegener, President

15. NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG

Paul T. Wegener, President

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set fourth in 21 CFR Part 56 will be responsible for initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

16. NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	17. SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	
Paul T. Wegener		
18. ADDRESS *(Number, Street, City, State and Zip Code)*	19. TELEPHONE NUMBER *(Include Area Code)*	20. DATE
3920 Goldfinch St San Diego, CA 92103	(619) 298-4279	6/18/98

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

Public reporting burden for this collection of information is estimated to average 100 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comment regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

[illegible] Reports Clearance Officer
[illegible]ework Reduction Project 0910-0014
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

Please DO NOT RETURN this application to this address.

EPITOME PHARMACEUTICALS LIMITED
3920 GOLDFINCH STREET, SAN DIEGO, CA 92103
TEL/FAX (619) 298-4279, PAUL@EPITOMEPHARM.COM

Ø Dr. Dölle
eil. 28.8.98

7 July, 1998

IND Submission

PolyPhenon E Ointment to treat genital warts

Confidential Information

2.0 Table of Contents

References in separate binders.

EXHIBIT 9
IND ACKNOWLEDGMENT LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

IND 56,401

Epitome Pharmaceuticals Limited
Attention: Paul T. Wegener, President
3920 Goldfinch Street
San Diego, CA 92103

JUL 29 1998

Dear Mr. Wegener:

We acknowledge receipt of your Investigational New Drug Application (IND) submitted pursuant to section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned: 56,401

Sponsor: Epitome Pharmaceuticals Limited

Name of Drug: Polyphenon Ointment

Date of Submission: July 7, 1998

Date of Receipt: July 14, 1998

Studies in humans may not be initiated until 30 days after the date of receipt shown above. If, within the 30-day waiting period, we identify deficiencies in the IND that require correction before human studies begin or that require restriction of human studies until correction, we will notify you immediately that the study may not be initiated ("clinical hold") or that certain restrictions must be placed on it. In the event of such notification, you must continue to withhold, or to restrict, such studies until you have submitted material to correct the deficiencies, and we have notified you that the material you submitted is satisfactory.

It has not been our policy to object to a sponsor, upon receipt of this acknowledgement letter, either obtaining supplies of the investigational drug or shipping it to investigators listed in the IND. However, if the drug is shipped to investigators, they should be reminded that studies may not begin under the IND until 30 days after the IND receipt date or later if the IND is placed on clinical hold.

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations). Those responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experience by telephone or fax no later than 7 calendar days after initial receipt of the information (21 CFR 312.32(c)(2)); (2) reporting any adverse experience with use of the drug that is both serious and unexpected in writing no later than 15 calendar days after initial receipt of the information (21 CFR 312.32(c)(1)); and (3) submitting annual

progress reports (21 CFR 312.33).

Please forward all future communications concerning this IND in triplicate, identified by the above IND number, and addressed as follows:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products, HFD-540
Attention: Document Control Room
5600 Fishers Lane
Rockville, Maryland 20857

Should you have any questions concerning this submission, please contact Millie Wright at (301) 827-2020.

Sincerely,

Mary J. Kozma-Fornaro
Supervisor, Project Management Staff
Division of Dermatologic and
Dental Drug Products, HFD-540
Office of Drug Evaluation V
Center for Drug Evaluation and Research

EXHIBIT 10
NDA SUBMISSION LETTER

MediGene

MediGene, Inc.
10660 Scripps Ranch Blvd., Suite 200
San Diego, CA 92131 USA
Tel. (858) 586-2240
Fax (858) 586-2241
www.medigene.com

September 23, 2005

Dr. Jonathan Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

RE: New Drug Application # 21-902
Polyphenon® E Ointment, 15%
Original Application

Dear Dr. Wilkin:

MediGene is hereby submitting NDA # 21-902 for Polyphenon® E Ointment, 15% for topical treatment in the indication external genital and perianal warts (*Condylomata acuminata*) in adult patients. Polyphenon® E Ointment, 15% contains a botanical drug substance derived from green tea leaves of *Camellia sinensis*. The proposed pharmacologic class of Polyphenon® E Ointment, 15% is immuno-modulatory.

MediGene plans to market Polyphenon® E Ointment, 15% as a prescription drug.

For the National Drug Code, MediGene has assigned 003-01 for the Product and Package Code (3-2 Product-Package configuration).

The NDA is a paper submission being provided in the Common Technical Document (CTD) format and contains the following modules and number of volumes:

Module 1 – Administrative Information and Prescribing Information (1 volume)
Module 2 – Common Technical Document Summaries (4 volumes)
Module 3 – Quality (10 volumes)
Module 4 – Nonclinical Study Reports (47 volumes)
Module 5 – Clinical Study Reports (231 volumes)

This original application contains a full archival copy in addition to the review copies listed below. A copy of Modules 1 and 2 is provided in each review copy.

- Quality review (Module 3 and an additional 3 copies of the Methods Validation Package)
- Nonclinical review (Module 4)
- Clinical (safety and efficacy) review (Module 5, Volumes 1 – 93 and 231)
- Clinical (pharmacology and pharmacokinetics) review (Module 5, Volumes 1 – 93 and 231)
- Statistical review (Module 5, Volumes 1 – 93 and 231)
- Botanical review (Modules 3, 4, 5)

Concurrent with this submission, the field copy containing Modules 1, 2 and 3 has been provided directly to the FDA Los Angeles District Office at 19701 Fairchild, Suite 300, Irvine, CA 92612. A field copy certification is provided in Section 1.3.3 in Module 1.

Polyphenon® E Ointment, 15% is the intended name for the drug product in this NDA. However, some parts of the development program have been performed in Europe, and therefore, the European naming convention (**Polyphenon® E 15% Ointment**) has been used in various documents throughout the NDA.

The botanical drug substance manufacturer, Mitsui Norin Co., Ltd., has applied for an International Non-Propriety Name (INN) for the active moiety Polyphenon® E through the World Health Organization. The application is still pending at this time.

Explanatory notes to individual modules:

Module 1

MediGene AG has received a waiver from FDA of the human drug application fee (PDUFA User Fee) for this NDA (# 21-902) under the small business waiver provision, § 736(d)(1)(D) of the Federal Food, Drug, and Cosmetic Act. A copy of the letter from FDA granting the waiver is provided in Module 1, Section 1.3.4 along with the User Fee Cover Sheet.

A request for waiver of a long-term (2-year) carcinogenicity study was submitted to the Agency on December 10, 2004 (IND # 56,401, Serial No. 057). A decision from FDA on the waiver request is still pending. A copy of the cover letter from the original long-term carcinogenicity waiver request is included in Module 1, Section 1.3.7.1. The cover letter has been updated to refer to study reports and literature references in the NDA rather than referring to documents in the IND. Edited references in the cover letter are shown in ~~strike-through~~ font with updated references immediately following in ***bold italics***.

Additionally, a request for full waiver of pediatric study requirements was submitted to the Agency on July 25, 2005 (IND # 56,401, Serial No. 063). As such, Polyphenon® E Ointment, 15% is intended to be prescribed for adult patients only. A copy of the pediatric waiver request is provided in Module 1, Section 1.3.7.2.

Module 3

The botanical drug substance manufacturer, Mitsui Norin Co., Ltd., has submitted a Drug Master File (DMF # 17964) to the Agency. Therefore, all sections of the NDA in Modules 2 and 3 pertaining to drug substance have been referred to the DMF and only limited information on the drug substance is provided in the NDA. A copy of the DMF letter of authorization from Mitsui Norin Co., Ltd. to FDA is provided in Module 1, Section 1.3.6.

As discussed with FDA in the pre-NDA meeting on January 24, 2005, stability data from the commercial manufacturer of Polyphenon® E Ointment, 15% is currently available through 6-months and is included in the NDA. Also provided is supporting stability data through 18 and 24 months for development (clinical) drug product manufactured by manufacturers other than the intended commercial manufacturer. The ointment formulation for the development (clinical) batches is identical to the to-be-marketed formulation. As requested by the Agency in the pre-NDA meeting, MediGene anticipates submitting 12-month stability data from the commercial manufacturer in December 2005 in order to support a longer shelf life than would be granted on the basis of the 6-month data submitted in the current NDA. Subsequently, 24-month stability data would be available and submitted to the Agency in December 2006. The intended shelf-life for Polyphenon® E Ointment, 15% is 24 months.

All facilities involved in the manufacture, packaging, and testing of both Polyphenon® E drug substance and Polyphenon® E Ointment, 15% are ready for inspection.

Module 5

Pursuant to 21 CFR § 314.50(f) and as requested in the pre-NDA meeting with FDA, hard copies of select case report forms (serious adverse events, early discontinuations, those excluded from per protocol analysis, lost to follow-up and others) are provided in the archival copy of the NDA (Module 5, Volumes 94 – 230).

Enclosed electronic files:

- The proposed draft text of the labeling and patient information in Module 1, Sections 1.4 (Prescribing Information) and 1.5 (Annotated Labeling Text) are provided electronically in Portable Document Format (PDF) and Microsoft Word format on Compact Disc (CD) in addition to the hard copy included in Module 1. The CD is labeled, **"Prescribing Information and Annotated Labeling Text"**.

- As confirmed with Millie Wright, Project Manager, FDA, CDER, ODE V, via email on July 12, 2005, it is acceptable to FDA that individual patient data listings (Module 5, Section 5.3.7.2) are provided on CD only. Enclosed is one CD containing individual patient data listings for all clinical studies included in the NDA (protocol numbers EPI-003, EPI-004, CT 1004, CT 1005, CT 1007, CT 1016, CT 1017, CT 1018, CT 1019). The CD is labeled, **"CTD Section 5.3.7.2 Individual Patient Data Listings"**.

- SAS transport files and data definition tables for raw and derived efficacy and safety data are provided on four CDs. The CDs are labeled, **"SAS Transport Files and Data Definition for Raw and Derived Efficacy and Safety Data"**.

- Electronic copies of text assessable files are provided for the following documents of the application on two CDs. The CDs are labeled, **"Clinical Study Reports, Protocols, Addenda (Searchable Adobe PDF and/or MS Word Files of Phase 3 Studies)"**.

  - Integrated Summary of Efficacy
  - Integrated Summary of Safety
  - Top-Line Statistical Report (CT 1017 and CT 1018 combined)
  - Clinical study reports, protocols and protocol amendments for the phase 3 studies CT 1005, CT 1017 and CT 1018.

All enclosed CDs have been virus checked.

Should you have any questions or comments, please do not hesitate to contact me at 858-586-2252 or by email at p.larson@medigeneUSA.com.

Sincerely,

Pam Larson
Sr. Manager, Regulatory Affairs
MediGene, Inc.

EXHIBIT 11
IND LOG

Polyphenon® E Ointment
Pre-IND Documentation

Date	Serial Number	Contents	TYPE
April 21, 1997	-	Epitome fax to FDA requesting documents on Condylox	Epitome Fax
April 21, 1997	-	Epitome F/U to conversation w/FDA re: telecon	Epitome Letter
May 9, 1997	-	Acknowledgement of receipt re: requested records	FDA Letter
May 28, 1997	-	Epitome letter to FDA requesting Guidance documents	Epitome Letter
June 12, 1997	-	Fax from Epitome to FDA requesting review of data ahead of meeting to discuss Phase II trial design *(Missing attachment)*	Epitome Fax
June 12, 1997	-	FDA fax External Constituents Request for Meeting	FDA Fax
June 13, 1997	-	FDA fax re: review of Phase II data	FDA Fax
July 2, 1997	-	Epitome fax to FDA requesting docs under Freedom of Information Act	Epitome Fax
July 8, 1997	-	Epitome fax to FDA concerning meeting requested	Epitome Fax
July 21, 1997	-	Letter from FDA acknowledging receipt of requested records	FDA Letter
July 25, 1997	-	Epitome fax to FDA requesting face-to-face meeting in September	Epitome Fax
August 12, 1997	-	Epitome fax to FDA requesting face-to-face meeting	Epitome Fax
September 29, 1997	-	Epitome letter to FDA re: Pre IND submission for Wart Heal *(Missing pages 4 and beyond in section 4 of submission package)*	Epitome Letter
October 17, 1997	-	Epitome fax to FDA (Dr. Wilkin) re: Wart Heal Meeting	Epitome Fax
October 19, 1997	-	Epitome fax to FDA re: Wart Heal Pre IND Meeting issues & resolutions	Epitome Fax
June 15, 1998	-	Epitome fax to FDA re: final preparation of IND submission	Epitome Fax

Polyphenon® E Ointment
Summary of FDA Communications
IND 56,401

Date	Serial Number	Contents	TYPE
July 7, 1998	000	IND *(Missing these sections:* • *Signed Form 1571 (draft version currently in files)* • *References)*	Submission
July 27, 1998	-	Epitome letter to FDA re: diskettes for Medical Reviewer *(Missing the diskettes)*	Epitome Letter
July 29, 1998	-	Letter from FDA acknowledging receipt of IND #56,401	FDA Letter
August 07, 1998	-	FDA Fax re: comments to PTLs	FDA Fax
August 08, 1998	-	Epitome fax to FDA Re: revisions to protocols	Epitome Fax
August 12, 1998	-	Fax to FDA Changes to PTL Re: Dr. Ko's comments *(Missing 5 pages of the fax (fax cover sheet indicates 11 pages total: only 6 pages are available in the current file))*	Epitome Fax
August 12, 1998	-	FDA Fax Memo Re: more changes to PTL	FDA Fax
August 12, 1998	001	IND Revisions *(Missing attachments to submission (revised protocols))*	Submission
August 12, 1998	-	Epitome Letter to FDA Re: questions to CMC	Epitome Letter
September 29, 1998	-	Epitome fax to FDA requesting discussion on Statistical, Pharm/Tox and Dose Ranging Issues	Epitome Fax
October 02, 1998	-	FDA Fax w/review comments to PTLs EPI-003 & 004	FDA Fax
October 30, 1998	-	Epitome Fax to FDA granting National Cancer Institute permission to cross reference IND *(Missing signed fax)*	Eptiome Fax
November 5, 1998	002	Epitome request to FDA for advice Re: CMC issues	Submission
November 25, 1998	-	Fax from FDA w/comments to chemistry & pharmacology	FDA Fax
December 1, 1998	-	FDA Fax Memo w/Dr. Ko's comments	FDA Fax
December 4, 1998	-	FDA Fax w/minutes from telecon on December 2, 1998	FDA Fax
January 4, 1999	003	Clinical Update *(Missing protocol EPI-004 dated 29 Nov 98)*	Submission
February 9, 1999	-	Submission of desk copies of Serial 003 *(Missing protocol EPI-004 dated 29 Nov 98)*	Submission

Date	Serial Number	Content	TYPE
March 29, 1999	-	Epitome fax revised CMC section	Epitome Fax
April 9, 1999	004	Revised Protocols *(Missing the following:* • *Protocol EPI-003 dated 23 Mar 99* • *List of changes to the protocols* • *Document comparison for revised protocols)*	Submission
April 16, 1999	-	Correction to Serial 004 *(Missing attachments)*	Letter
July 8, 1999	-	FDA Fax re: Pharm/Tox review comments	FDA Fax
December 13-21, 1999 (telecon date unknown)	-	Epitome minutes of telecon with FDA	Telecon minutes
December 21,1999	005	Faxed Copy of Annual Report – effective 8/29/99	Fax Submission
January 13, 2000	-	Fax to FDA (from Epitome) Re: trials with another formulation *(Missing fax)*	Epitome Fax
January 26, 2000	006	Revised Protocols *(Missing disk)*	Submission
April 27, 2000	006	Transfer of Responsibility from Epitome to MediGene/Waldman Biomedical Consultancy (WBC)	Submission
April 27, 2000	-	Desk copy of Serial 006 (transfer of responsibilities) to Millie Wright	Letter
April 27, 2000	-	Submission of desk copy of Letter for Transfer of Responsibility from Epitome to MediGene/WBC	Submission
June 10, 2000	007	Support documents for WBC to represent MediGene, AG *(Missing form FDA 1571)*	Submission
Date ??? June 10, 2000	-	FDA Letter Re: Transfer of responsibility from Epitome to MediGene *(No date, missing appended signature page)*	FDA Letter
December 20, 2000	008	Annual Report- 12/20/00	Submission
January 29, 2001	-	Request for Guidance letter from I. Gander, MediGene AG to FDA *(Missing letter)*	Letter
March 20, 2001	-	Letter to FDA re: MediGene request for a Type C Guidance Meeting *(Missing signed letter from Waldman)*	Waldman Letter
March 27, 2001	009	Fax Submission of FDA 1571 to support request for meeting letter submitted on 3/20/01	Fax Submission
March 27, 2001	010	Fax Submission of FDA 1571 to support Request for Guidance letter submitted by Dr. I. Gander on 1/29/01	Fax Submission

Date	Serial Number	Content	TYPE
March 27, 2001	009 & 010	Submission of FDA 1571s for Serial 009 (Request for Meeting) and Serial 010 (Request for Guidance)	Submission
March 29, 2001	-	Letter to FDA Re: MediGene Acceptance of Transfer of the IND (file attachments were reconstructed from previous submissions)	Waldman Letter
May 11, 2001	-	Information Package (dated May 10, 2001) to FDA Re: Type C Meeting	Information Package
May 16, 2001	-	Corrected Version of Attachment J-Information Package for Type C Meeting	Waldman Letter
June 11, 2001	-	Minutes from MediGene Guidance Meeting w/FDA 6/11/01	Meeting Minutes (internal)
June 11, 2001	-	Executive Summary to Guidance Meeting with FDA on 6/11/2001	Summary (internal)
August 13, 2001	-	Meeting Minutes for 6/11/01	FDA Fax
August 17, 2001	011	Request for an End of Phase 2 Meeting/pre-Phase 3 Meeting	Fax Submission
August 22, 2001	012	Request for Review of Draft Preclinical Protocol	Fax Submission
October 16, 2001	-	Letter to FDA-review of Minutes	Waldman Letter
October 19, 2001	013	Information Package for Type B, End of Phase 2/pre-Phase 3 Meeting	Submission
November 19, 2001	-	Reviewers Comments re: Sponsor's Meeting Package Submitted 10/19/01	Reviewers Comments
November 19, 2001	-	Register of Meeting Participants-meeting between FDA & MediGene	Participant Log
November 19, 2001	-	MediGene Minutes from the End of Phase 2 Meeting w/FDA	Meeting Minutes (internal)
December 11, 2001	014	Minutes End of Phase 2/ pre-Phase 3 Meeting	Submission
December 20 2001	015	Annual Report – 2001	Submission
December 21, 2001	016	Letter to FDA requesting teleconference	Waldman Letter
December 26, 2001	-	Letter to FDA re: MediGene review of comments from FDA *(Missing signed letter from Waldman)*	Waldman Letter
January 23, 2002	017	Withdrawal of Telecon Request Submission 016	Submission
February 11, 2002	018	Informational Amendment: Clinical Final Study Report	Submission
February 12, 2002	019	Information Amendment: Pharm/Tox	Submission
February 14, 2002	020	Request Special Protocol Assessment-Phase 3	Submission
February 20, 2002	021	Request Special Protocol Assessment-Preclinical Trial PTLs	Submission

Date	Serial Number	Contents	TYPE
March 6, 2002	022	Withdrawal of a Special Protocol Assessment Submission 020	Submission
March 13, 2002	-	Letter to FDA requesting Meeting for Phase 3 *(Waldman letter is not signed nor on letterhead (the copy in the files appears to be a draft – it is unclear if this was ever submitted to FDA))*	Waldman Letter
March 18, 2002	023	Request for a Meeting Phase-3	Submission
March 25, 2002	024	Information Package for Meeting on Global Clinical Issues	Submission
April 17, 2002	-	Fax from FDA Re: Meeting Minutes for 11/19/01	FDA Fax
April 17, 2002	-	Fax from FDA Re: clinical reviewer comments on Serial 018	FDA Fax
April 17, 2002	-	Fax from FDA Re: comments on Serial #023	FDA Fax
April 18, 2002	-	Letter to FDA Re: Notification that Jane Campbell is authorized to act on behalf of WBC for any matters related to IND 56,401 *(Missing letter)*	Waldman Letter
April 19, 2002	-	Letter from FDA Re: Serial 020 and Clinical Trials Database	FDA Letter
April 29, 2002	025	Information Amendment – Submission of FDA 1571 for Waldman Letter dated April 18, 2002	Submission
May 1, 2002	026	Request for a Special Protocol Assessment Phase 3	Submission
May 21, 2002	-	FDA Letter Re: Receipt and acceptance of Serial 026, Special Protocol Assessment	FDA Letter
June 12, 2002	-	Fax from FDA Re: Reviewers comments (dated June 10, 2002) to Serials 019, 021, 026	FDA Fax
June 12, 2002	-	Fax from FDA Re: Copy of letter on Special Protocols, Serial 026	FDA Fax
June 12, 2002	-	Letter from FDA concerning Serial 026 requesting Special PTL Assessment For Phase 3	FDA Letter
June 21, 2002	-	Letter from FDA concerning submission 026 and Clinical Trials Data Bank	FDA Letter
June 28, 2002	027	MediGene AG Response to FDA Comments on Special PTL Assessment (Serial 026)	Submission

Date	Serial Number	Contents	TYPE
June 28, 2002	-	Fax to FDA concerning response to FDA comments on Special PTL Assessment *(Missing fax (this fax is referenced in the fax sent on July 1, 2002))*	Waldman Fax
July 1, 2002	-	Fax to FDA-concerning response to FDA comments to Phase 3 (fax attachments were reconstructed from June 28, 2002 submission of Serial 027)	Waldman Fax
August 15, 2002	028	Information Amendment and response to FDA comments (dated June 10, 2002) to Serials 019, 021, 026	Submission
August 20, 2002	029	MediGene AG response to FDA's preclinical recommendations	Submission
September 06, 2002	-	Fax from FDA w/comments from Stats reviewer for Serial 027	FDA Fax
September 11, 2002	030	Information Amendment CMC	Submission
October 7, 2002	031	Information Amendment Clinical & Preclinical	Submission
November 29, 2002	032	Update to Serial 031, page replacement	Submission
December 18, 2002	033	Information Amended- Pharmacology & Toxicology	Submission
December 23, 2002	034	2002 Annual Report	Submission
December 24, 2002	-	Fax from FDA – Statistics Comments regarding Serial 031	FDA Fax
December 30, 2002	035	Information Amendment Proposal to use Hochberg procedure for statistical analysis plan	Submission
January 30, 2003	036	Request for Guidance regarding use of second supplier for API	Submission
March 18, 2003	-	Record of FDA communication (phone call received by WBC)	Emailed Phone Record
May 29, 2003	037	Transfer of regulatory responsibility	Submission
July 9, 2003	-	Fax from FDA – Stats reviewer comments on Serial 035	FDA Fax
July 29, 2003	038	Protocol Amendment - CT1018 Addition of Clinical Investigators	Submission
July 30, 2003	-	Record of Regulatory Agency Communication (Becky Donahue)	Phone Record
July 31, 2003	-	Record of Regulatory Agency Communication (Becky Donahue)	Phone Record
August 1, 2003	039	Response to Serial No. 038 Electronic Copy of Protocol CT1018	Submission
September 3, 2003	040	Protocol Amendment – CT1018 Addition of New Investigator (Gall)	Submission
October 23, 2003	041	Protocol Amendment – CT1018 Addition of New Investigator (Hemsell)	Submission

Date	Serial Number	Content	TYPE
November 3, 2003	042	Annual Report	Submission
November 04, 2003	043	Change of MediGene, Inc. phone and fax numbers	Submission
December 2, 2003	044	Protocol Amendment – Addition of New Investigator (Strober)	Submission
December 19, 2003	045	15-Day Safety Report – SAE (pustular vulvovaginitis) at Colombian Site	Submission
January 9, 2004	046	Change of Address	Submission
February 13, 2004	047	Protocol Amendment – New Clinical Investigators (Non-U.S. sites)	Submission
February 26, 2004	048	Protocol Amendment – New Clinical Investigator (Dr. Cheryl Gibson, site USA-10, replaces Dr. Thomas)	Submission
April 6, 2004	049	Protocol Amendment – Updated 1572's & New Labels	Submission
April 26, 2004	-	Request for SLI Carcinogenicity Study (FOIA Request)	Fax to FDA
May 4, 2004	-	Request for SLI Study must be sent directly to NCI (FOIA Request)	Phone Record
May 5, 2004	-	Request for SLI Carcinogenicity Study (FOIA Request)	Fax to NCI
May 6, 2004		Response to May 5, 2004 fax to NCI	Letter from NCI
May 11, 2004	050	Information Amendment – Updated 1572 (Dr. Higareda-Almaraz, Mexico)	Submission
June 7, 2004	051	Information Amendment – Updated 1572 (Dr. Caracas, Romania)	Submission
August 3, 2004	052	Protocol Amendment – New & Updated 1572s	Submission
August 31, 2004	-	Pre-NDA Meeting	Phone Record
November 3, 2004	-	Pre-NDA Meeting – Official Request	Phone Record
November 3, 2004	053	Request for a Type B Meeting – Pre-NDA Meeting	Submission
November 5, 2004	-	Pre-NDA Meeting – Discussion of meeting type and tentative date	Phone Record
November 9, 2004	054	Annual Report	Submission
November 9, 2004	-	Confirmation of pre-NDA meeting date (January 24, 2005)	FDA Email
November 11, 2004	-	Acknowledgement of FDA email	Email to FDA
November 15, 2004	-	FDA correspondence: Type B meeting scheduled for January 24, 2005, 1:00 – 2:00 pm	FDA Letter
November 30, 2004	055	Preclinical Amendment	Submission
December 03, 2004	056	Information Amendment-CMC	Submission
December 06, 2004	-	Pre-NDA Meeting Agenda Email	Email to FDA
December 06, 2004	-	Response from FDA-Pre-NDA Meeting	Email from FDA
December 07, 2004	-	Pre-NDA Meeting Logistics email	Email to FDA
December 10, 2004	057	Request for Carcinogenicity waiver	Submission

Date	Serial Number	Contents	Type
December 17, 2004	058	Pre NDA Meeting Package	Submission
December 20, 2004	-	Pre NDA Meeting Package	Phone Record
December 29, 2004	-	Request for Summary Basis of Approval for Aldara (imiquimod) Cream, 5% (FOIA Request)	Fax to FDA
January 03, 2005	-	Receipt of FOIA request	Letter from FDA
January 21, 2005	059	Pre NDA Meeting List of Attendees	Submission
January 21, 2005	-	Fax of Pre NDA List of Attendees to M. Wright (Serial 059)	Fax to FDA
January 21, 2005	-	Pre NDA Meeting Package Comments	Fax from FDA
January 24, 2005	-	Pre NDA Register of Meeting Participants	Meeting with FDA
February 2, 2005	-	FOIA Response Summary Basis of Approval for Aldara	Letter from FDA
February 4, 2005	060	General Correspondence MediGene Pre-NDA Meeting Minutes	Submission
February 8, 2005	-	Correspondence from FDA re: setting up secure email for NDA	Fax from FDA
February 9, 2005	-	Telecon with Millie Wright re: secure email	Phone Record
February 11, 2005	-	Email to W. Lee re: setting up secure email	Email to FDA-
February 14, 2005	-	Email from W. Lee-Secure email guide	Email from FDA
February 14, 2005	-	Email to W. Lee-Secure Email Guide correspondence	Email to FDA
February 16, 2005	-	Fax from M. Wright Official Minutes Pre-NDA Meeting	Fax from FDA
February 18, 2005	-	Letter from FDA including Official Meeting Minutes from Pre-NDA	Letter from FDA
February 24, 2005	-	Telecon with Sandy Childs re: Information on Submission Date for NDA	Phone Record
February 25, 2005	-	Email to M. Wright re: Electronic Format	Email to FDA
February 25, 2005	-	Telecon with CDER Document Room re: Pre-assigned NDA Number	Phone Record
February 25, 2005	-	Email to Sandy Childs re: phone number for Document Control Room	Email to FDA
February 25, 2005	-	Email response from Sandy Childs with Telephone number to Document Control Room	Email from FDA
March 30, 2005	-	Email to M. Wright re: Number of Copies of NDA	Email to FDA
April 1, 2005	-	Email from M. Wright out of the office	Email from FDA
April 1, 2005	-	Email to M. Wright acknowledging out of the office and will follow-up next week	Email to FDA

Date	Serial Number	Content	TYPE
April 7, 2005	-	Telecon with Millie re: Electronic format for NDA, Number of Volumes, Carcinogenicity waiver	Phone Record
April 21, 2005	-	Email to Millie regarding binder colors for NDA	Email to FDA
May 11, 2005	-	Request for Waiver of Application Fee	Letter to FDA
May 23, 2005	061	General Correspondence: Change of MediGene Authorized Representative	Submission
May 23, 2005	-	Copy of Serial 061 Cover Letter to M. Wright	Letter to FDA
May 25, 2005	062	General Correspondence: Clinical Long-term safety evaluation	Submission
June 22, 2005	-	Telecon with Millie re: NDA binder colors	Phone Record
June 23, 2005	-	Teelcon with Beverly Friedman re: PDUFA User Fee Waiver Request	Phone Record
June 24, 2005	-	Amendment to Request for Waiver of Application Fee Submitted on May 11, 2005	Submission
June 29, 2005	-	Telecon with Beverly Friedman re: MediGene AG's affiliates	Phone Record
June 29, 2005	-	Email to Beverly Friedman regarding MediGene AG's affiliates	Email to FDA
June 30, 2005	-	Reply Email from Beverly Friedman response received	Email from FDA
June 30, 2005	-	Email to Millie re: NDA Patient Data Listings	Email to FDA
July 12, 2005	-	Email from FDA: Response NDA Patient Data Listings	Email from FDA
July 25, 2005	063	Request for waiver of Pediatric Studies	Submission to FDA
September 06, 2005	-	Letter from FDA granting approval of the small business waiver of the application fee for NDA 21-902	Letter from FDA
October 11, 2005	-	Telecon with Millie Wright	Phone Record
October 11, 2005	-	Email to Millie Wright re: FDA address change	Email to FDA
October 11, 2005	-	Email from Millie Wright re: FDA change of address	Email from FDA
November 10, 2005	064	Annual Report	Submission to FDA

EXHIBIT 12
NDA LOG

Polyphenon® E Ointment, 15%
FDA Correspondence and Submission Summary
NDA 21-902

Date	Submission Number	Contents	TYPE
September 23, 2005	001	NDA Submission	Submission
September 23, 2005	-	NDA Field Copy Submission	Submission
October 11, 2005	-	Telecon with Millie Wright, re: receipt of NDA, new acting Division Director	Phone Record
October 11, 2005	-	Email to Millie Wright, re: Central Document Room address change	Email to FDA
October 11, 2005	-	Email from Millie Wright re: Central Document Room address	Email from FDA
November 16, 2005	-	Email to Millie Wright, re: PL out of office	Email to FDA
November 28, 2005	-	Telecon with Robert Hummel, re: NDA	Phone Record
November 29, 2005	-	Telecon with Robert Hummel, re: NDA telecon	Phone Record
November 29, 2005	-	Email to Robert Hummel, re: NDA telecon	Email to FDA
November 30, 2005	-	Email from Robert Hummel, re: INN / USAN status	Email from FDA
November 30, 2005	-	Telecon with FDA, re: INN /USAN status	Phone Record
December 2, 2005	-	Telecon with FDA, re: NDA CMC Questions – Manufacturers, PE Testing	Phone Record
December 2, 2005	-	Email to FDA, re: Follow-up from telecon	Email to FDA
December 8, 2005	-	Telecon with FDA, re: USAN Application	Phone Record
December 8, 2005	-	Fax from FDA, re: Filing Communication	Fax from FDA
December 9, 2005	002	CMC Amendment: Tabular Summary of Manufacturers, PE Testing	Submission
December 14, 2005	-	Email from FDA, re: Response to voicemail on CMC question (characterization)	Email from FDA
December 14, 2005	-	Email to FDA, re: Request for clarification on CMC question #3 in Filing Communication (characterization)	Email to FDA
December 14, 2005	-	Email from FDA, re: Schedule telecon to discuss CMC question # 3 (characterization)	Email from FDA
December 15, 2005	-	Telecon with FDA, re: clarification on CMC Question #3 in filing communication	Phone Record
December 16, 2005	-	Letter from FDA-Filing Communication dated Dec. 8, 2005 (Original hard copy)	Letter from FDA
December 22, 2005	-	Email to Millie Wright, re: update on USAN name	Email to FDA
December 29, 2005	-	Email to Millie Wright, re: Stability Amendment Update	Email to FDA
January 4, 2006	-	Telecon with FDA, re: Clinical Site Inspection CT 1017 – Russian Site # 1	Phone Record
January 5, 2006	-	Email to Millie Wright, re: Follow-up to Phone Record –Russian Site Information	Email to FDA

Date	Submission Number	Contents	TYPE
January 6, 2006	003	Response to Filing Communication	Submission
January 16, 2006	004	Response to FDA email 11/30/05, re: USAN and INN Status	Submission
January 17, 2006	-	Email from R. Hummel, re: USAN Status and additional CMC questions	Email from FDA
January 17, 2006	-	Email response to R. Hummel, re: USAN Status and additional CMC questions	Email to FDA
January 23, 2006	-	Email Confirmation of PDUFA date	Email from FDA
January 25, 2006	-	Phone call with Millie Wright – Clinical Site Audits and Miscellaneous	Phone Record
January 26, 2006	-	Email information of CT 1018 Chile # 4 and US # 9 sites	Email to FDA
January 26, 2006	-	Additional Copies of NDA 21-902 Submission 003 to M. Wright	Submission of Desk Copies to FDA
January 27, 2006	-	Telecon with Dr. Rajiv Agarwal, CMC Reviewer, re: Batches Used in Pivotal Clinical Studies	Phone Record
January 30, 2006	005	CMC Amendment - Addition of 12 Month Stability Data for Ointment	Submission
February 1, 2006	-	Telecon with Roy Blay, Ph.D., Office of Medical Policy, re: Information request in preparation for Clinical Site Audits	Phone Record
February 1, 2006	-	Email to M. Wright, re: Meaning of "E" in Polyphenon® E	Email to FDA
February 1, 2006	-	Email to R. Hummel, re: test for heavy metals and arsenic JP vs. USP	Email to FDA
February 1, 2006	-	Fax from M. Wright, re: Clinical and Statistical Questions	Fax from FDA
February 3, 2006	006	Supplemental Form FDA 356h	Submission
February 7, 2006	-	Email from R. Hummel, re: Dr. Agarwal's advice regarding USP vs. JP methods	Email from FDA
February 14, 2006	-	Telecon with Millie, re: changing the drug product trade name	Phone Record
February 16, 2006	007	CMC Amendment-Response to email questions from FDA 1/17/06	Submission
February 16, 2006	008	Response to DSI (Roy Blay) requests on 2/1/06, Clinical Site Information	Submission
February 22, 2006	-	Email from R. Hummel, re: CMC Batch Info.	Email from FDA
February 22, 2006	009	Clinical Site Information (Letters of Assurance)	Submission
February 23, 2006	-	Voice message from Roy Blay, re: Follow-up to email	Phone Record

Date	Submission Number	Contents	TYPE
February 28, 2006	-	Email to Millie Wright, re: Label Mock-ups	Email to FDA
February 28, 2006	010	CMC Amendment - Response to FDA Email Dated February 22, 2006	Submission
March 1, 2006	-	Fax from M. Wright, re: Clin. Pharm./CMC question; clarification to Feb. 22 fax	Fax from FDA
March 1, 2006	-	Telecon with Dr. Rajiv Agarwal, re: Add'l batch info; update on USAN application	Phone Record
March 2, 2006	011	CMC Amendment-Response to Phone Request on March 1, 2006	Submission
March 6, 2006	012	Clinical/Statistical Amendment: Response to FDA Fax Dated Feb.1, 2006	Submission
March 8, 2006	-	Telecon with Millie Wright, re: status of clin./stat. questions, trade names	Phone record
March 8, 2006	-	Telecon with Rajiv Agarwal, re: Add'l CMC Requests - API blending, 10% ointment	Phone Record
March 28, 2006	-	Email to Rajiv Agarwal, re: NDA 21-902, Response to Phone Inquiry of 3/8/06	Email to FDA
April 7, 2006	-	Fax from FDA, re: Clinical reviewer request for drug product samples	Fax from FDA
April 17, 2006	013	CMC Amendment – Submission of Comparability Protocol for Addition of Second Drug Substance Manufacturing Site	Submission
April 18, 2006	-	Email to FDA (copy of Submission 013) and response from R. Hummel, re: Goldie, Scott, new CMC Project Manager	Email to and from FDA
April 18, 2006	014	Response to FDA Fax Dated April 6, 2006 - Drug Product Samples	Submission
April 18, 2006	015	Addendum to Response to Filing Communication Submitted on January 6, 2006 (Submission No. 003)	Submission
April 20, 2006	016	Response to Clinical Pharmacology/CMC Fax of March 1, 2006	Submission
April 20, 2006	017	CMC Amendment – Response to FDA Phone Inquiry on March 8, 2006	Submission
April 20, 2006	-	Telecon with Millie Wright, re: status of trade names, 10% ointment data, misc.	Phone record
April 21, 2006	018	CMC Amendment – Additional Response to Filing Communication dated 12/8/2005, Identity and Assay for Excipient Oleyl Alcohol	Submission
April 21, 2006	-	Telecon with Millie Wright, re: Comparability Protocol and Trade Names	Phone record
April 25, 2006	019	Labeling Amendment	Submission

Date	Submission Number	Contents	TYPE
April 26, 2006	-	Telecon with Millie Wright, re: update 10% Ointment Stability Data, Worldwide Marketing Status, CT1005	Phone record
April 27, 2006	-	Email to Millie Wright in response to Dr. Papadopoulos' questions	Email to FDA
April 28, 2006	-	Email from Millie Wright, re: request for raw data for Dr. Papadopoulos	Email from FDA
April 28, 2006	-	Email from Millie Wright, re: request for batch analysis of 10% drug product (Haupt) & comparison (10% vs. 15%)	Email from FDA
April 28, 2006	-	Email to Millie Wright with additional information in response to Dr. Papadopoulos' questions	Email to FDA
April 28, 2006	-	Fax from Irma Rivera at FDA to propose inspection dates for two manufacturing facilities in Germany	Fax from FDA
May 1, 2006	020	Clinical Amendment – Response to Questions from Dr. Elektra Papadopoulos	Submission
May 3, 2006	021	General Correspondence – Clarification to Submission No. 013, CMC Amendment	Submission
May 5, 2006	022	Clinical Amendment – CT 1005 Site 45 Raw Data Requested by Dr. Elektra Papadopoulos	Submission
May 18, 2006	023	CMC Amendment – Response to Chemistry Reviewer Request 10% Batch Data & Stability	Submission
May 22, 2006	-	Telecon with Millie Wright, re: FDA request for telecom to discuss questions from clinical & statistical reviewers	Phone record
May 22, 2006	-	Fax from Millie Wright at FDA with CMC reviewer information request	Fax from FDA
May 22, 2006	-	Fax from Millie Wright at FDA re: Telecon, May 23 at 4:30 PM	Fax from FDA
May 23, 2006	-	Fax from Millie Wright at FDA re: CMC Reviewer Questions	Fax from FDA
May 23, 2006	-	MediGene internal minutes – Telecon with Millie Wright, et al re: Reproduction of efficacy results & generation of relapse data	Phone record
May 26, 2006	024	Clinical Amendment – Response to Clinical/Statistical Questions in FDA Fax Dated May 22, 2006	Submission
June 2, 2006	025	Clinical Site Information, Correction to Amendment # 008 (February 16, 2006). Copy to Roy Blay.	Submission
June 5, 2006	-	Telecon with Millie Wright at FDA re: Follow-up to Clin/Stat Submission # 024	Phone record

Date	Submission Number	Contents	TYPE
June 6, 2006	026	CMC Amendment – Response to FDA CMC Information Requests via Fax Memorandums, Dated May 22, 2006 and May 23, 2006	Submission
June 12, 2006	-	Telecon with Millie Wright at FDA re: Status of Clin/Stat Submission # 024	Phone record
June 22, 2006	027	General Correspondence – New Medigene Authorized Representative	Submission
June 22, 2006	-	Telecon with Millie Wright at FDA, re: USAN update and FDA request for telecon	Phone record
June 23, 2006	-	Response To Request for 3 Desk Copies each of the ISS and ISE	Mail Correspondence to FDA
June 26, 2006	-	PDUFA Extension Letter	Fax from FDA
June 26, 2006	-	Meeting Minutes: Status of NDA – FDA Meeting Via Teleconference	Teleconference Meeting Minutes
June 29, 2006	-	CMC Information Request	Fax from FDA
June 29, 2006	-	PDUFA Extension Letter	Letter from FDA
June 29, 2006	-	Suggested USAN Name	Letter from USAN Council
July 10, 2006		CP.001/Labeling Negotiations/CMC/Clinical-Biostatistics Review Status	Phone Record
July 11, 2006	028	General Correspondence: CMC Information Request Rationale	Submission
July 13, 2006	-	Accepted Trade Name	Fax from FDA
July 18, 2006	-	CMC Information Request Rationale/10% or 15% Formulation Review Status	Phone Record
July 24, 2006	029	General Correspondence: Clinical/Statistics Review Status	Submission
July 27, 2006	-	CMC Information Request Rationale Follow-up/120-Day Safety Update	Phone Record
August 01, 2006	-	CMC Information Request Rationale FDA Teleconference/120-Day Safety Update/Labeling Amendment	Phone Record
August 01, 2006	-	FDA Official Meeting Minutes of August 1st TC on DS and DP Specs	Letter from FDA
August 02, 2006	030	Safety Update	Submission
August 09, 2006	031	CMC Amendment – Response to FDA Fax Memorandum Dated June 28, 2006	Submission
August 10, 2006	032	Label Amendment	Submission

Date	Submission Number	Contents	TYPE
August 14, 2006	-	CMC Amendment Correction/August 23 FDA-MNK Meeting	Phone Record
August 14, 2006	033	CMC Amendment Correction	Submission
August 14, 2006	034	NDA Amendment - Type A Meeting Request	Submission
August 16, 2006	035	Type A Briefing Document	Submission
August 18, 2006	036	General Correspondence: Change of Contact Information	Submission
August 18, 2006	-	CMC phone Request (Placebo)	Phone Record
August 18, 2006	037	CMC Amendment: Response to Phone Request on August 18, 2006	Submission
August 23, 2006	-	Type A Meeting Request/Clinical-Statistical Review Status	Phone Record
August 29, 2006	-	Request for Desk Copies of Type A Meeting Briefing Package	Mail Correspondence to FDA
August 29, 2006	-	Type A Meeting/ CMC Reviewers' Comments for August 16th Meeting Package	Phone Record
August 29, 2006	-	CMC Reviewers' Comments for August 16th Meeting Package	Fax from FDA
September 5, 2006	-	Request for Teleconference - Regulatory Options	Phone Record
September 07, 2006	-	Teleconference Status – Regulatory Options	Phone Record
September 08, 2006	-	Teleconference Meeting Minutes – Regulatory Options	Teleconference Meeting Minutes
September 08, 2006	-	FDA Official Meeting Minutes of Sept 08 TC on DS and DP specs	Letter from FDA
September 14, 2006	038	Regulatory options Response and TC Meeting Minutes	Submission
September 14, 2006	-	Clinical Information Status/USAN/SPL/Regulatory Options Response	Phone Record
September 19, 2006	-	TC Request to Regulatory Options Response	Phone Record
September 21, 2006	-	Teleconference Meeting Minutes – Submission 038 Response	Teleconference Meeting Minutes
September 27, 2006	-	CMC Amendment Status/Phase 4 Study Info/USAN Name/ALPS CP/Label Negotiations	Phone Record
September 28, 2006	039	CMC Amendment - CMC Pending Info	Submission
September 29, 2006	-	Container and Carton Label Changes	Fax from FDA
October 04, 2006	-	CMC Info Request – Sept 28 CMC Amendment	Fax from FDA

Date	Submission Number	Contents	TYPE
October 04, 2006	040	CMC Amendment – CMC Information Request to Submission 039	Submission
October 04, 2006	-	Label Request	Fax from FDA
October 05, 2006	041	Label Amendment – Response to October 04 Label Request	Submission
October 06, 2006	042	CMC Amendment – Updated CPM Test Instruction	Submission
October 06, 2006	-	Labeling Clinical Information Request	Fax from FDA
October 10, 2006	043	Label Amendment – Response to October 06 Clinical Information Label Request	Submission
October 12, 2006	-	Container/carton label change status/Phase 4 Study Info status/ALPS CP	Phone Record
October 12, 2006	-	August 1st FDA Official Meeting Minutes	Fax from FDA
October 13, 2006	044	Label Amendment – Response to Container/Carton Label Change	Submission
October 16, 2006	-	Container/Carton Label Change – Storage Temperature	Fax from FDA
October 16, 2006	-	Container/Carton Storage Temperature Label Change/Phase 4 Study Info	Phone Record
October 16, 2006	-	Phase 4 Post-marketing Studies	Fax from FDA
October 17, 2006	-	Container/Carton Storage Temp Label Response	Fax from FDA
October 18, 2006	-	Container/Carton Storage Temp Label Questions/Phase 4 Study Teleconference	Phone Record
October 18, 2006	-	FDA Response to Container/Carton Storage Temp	Email from FDA
October 19, 2006	-	Draft Labeling	Phone Record
October 19, 2006	-	Draft Labeling – Word copies of FDA proposed PI and PPI	Email from FDA
October 19, 2006	-	TC Meeting Minutes – Phase 4 Study Fax Memo	Teleconference Meeting Minutes
October 20, 2006	-	Label Negotiations TC w/ FDA and Phase 4 Draft Protocol	Email to FDA
October 20, 2006	-	Label Negotiations TC w/ FDA and Phase 4 Draft Protocol Response	Email from FDA
October 20, 2006	-	USAN Name	Email from FDA
October 23, 2006	-	Phase 4 Draft Proposal	Email to FDA (not a submission)
October 23, 2006	045	Label Amendment - Response to Container/Carton Storage Temperature Statement	Submission
October 24, 2006	046	Label Amendment – Response to Oct 19 FDA-Proposed Draft Labeling	Submission
October 24, 2006	-	Draft Labeling/Action Letter	Phone Record

Date	Submission Number	Contents	TYPE
October 25, 2006	-	Label Negotiations TC	Email from FDA
October 25, 2006	-	Label Negotiations TC/Phase 4 Draft Proposal for PK Study	Phone Record
October 25, 2006	-	Phase 4 Draft Proposal For PK Study	Email to FDA (not a submission)
October 26, 2006	-	PI-PPI Labeling/Phase 4 PK Study	Phone Record
October 26, 2006	047	General Correspondence - MediGene's Agreement to Phase 4 Commitment (PK Study)	Submission
October 26, 2006	-	FDA-Proposed PI Draft Labeling	Email from FDA
October 26, 2006	-	MediGene-Proposed PI Draft Labeling	Email to FDA (not a submission)
October 27, 2006	-	PI Draft Label Proposal	Phone Correspondence
October 27, 2006	048	General Correspondence - MediGene's Agreement to Veregen™ Final Labeling	Submission
October 30, 2006	-	Veregen Labeling - Indication	Email from FDA
October 30, 2006	-	Veregen Labeling - Indication	Email to FDA
October 30, 2006	-	Final Label	Phone Record
October 30, 2006	049	General Correspondence – Resubmission of MediGene's Agreement to Veregen Labeling	Submission
October 31, 2006	-	NDA Action Letter – Approval Letter	Fax from FDA
October 31, 2006	-	NDA Approval Letter	Phone Record
November 01, 2006	-	NDA Approval Letter – Complete Refax	Fax from FDA
November 08, 2006	050	Safety Update	Submission

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